Medical Library

MAY 27 1942

AMERICAN HEART JOURNAL

For the Study of the

CIRCULATION

Published Monthly Under the Editorial Direction of
The American Heart Association

Vol. 23 MAY 1942 No. 5

FRED M. SMITH----------Editor-in-Chief

Associate Editors

HUGH McCULLOCH
HORACE M. KORNS
EDGAR V. ALLEN

EDITORIAL BOARD

CLAUDE S. BECK
NORMAN E. FREEMAN
HARRY GOLDBLATT
GEORGE HERRMANN
WILLIAM J. KERR
ROBERT L. LEVY
H. M. MARVIN
JONATHAN C. MEAKINS
ROY W. SCOTT
ISAAC STARR
J. MURRAY STEELE
PAUL D. WHITE
FRANK N. WILSON
CHARLES C. WOLFERTH
IRVING S. WRIGHT

Published by THE C. V. MOSBY COMPANY, 3525 Pine Blvd., St. Louis, U.S.A.
Copyright 1942 by The C. V. Mosby Company

Contents on Inside Cover

American Heart Journal

For the Study of the Circulation

CONTENTS FOR MAY, 1942

Original Communications

The Graphic Registration of the Normal Heart Sounds. Maurice B. Rappaport, E. E., and Howard B. Sprague, M.D., Boston, Mass. ---- 591

Observations on the Effect of Tourniquets on Acute Cardiac Crises, Normal Subjects, and Chronic Heart Failure. William B. Kountz, M.D., John R. Smith, M.D., and Sydney T. Wright, M.D., St. Louis, Mo. ---- 624

The Influence of Xanthine Drugs and Atropine on the Mortality Rate After Experimental Occlusion of a Coronary Artery. George V. LeRoy, M.D., G. K. Fenn, M.D., and N. C. Gilbert, M.D., Chicago, Ill. ---- 637

A Critique of the Plethysmographic Method of Measuring Blood Flow in the Extremities of Man. M. Landowne, M.D., and L. N. Katz, M.D., Chicago, Ill. ---- 644

The Internal Pneumocardiogram. Aldo Luisada, M.D., Boston, Mass. ---- 676

Electrocardiographic Changes in Bronchial Asthma and Their Significance. Joseph Harkavy, M.D., and Alfred Romanoff, M.D., New York, N. Y. ---- 692

Department of Clinical Reports

Recent Myocardial Infarction Followed by Involvement of the Joints of the Hand and Wrist. Joseph C. Meyer, M.D., and Herbert F. Binswanger, M.D., Chicago, Ill. ---- 715

Coronary Disease in the Ape. G. W. Manning, M.D., Toronto, Canada ---- 719

Department of Reviews and Abstracts

Selected Abstracts ---- 725

Book Reviews ---- 736

American Heart Association, Inc. ---- 738

Vol. 23, No. 5, May, 1942. American Heart Journal is published monthly by the C. V. Mosby Company, 3523 Pine Blvd., St. Louis, Mo. Subscription Price: United States, its Possessions, Pan-American Countries, $10.00; Canada, $11.50 (Canadian Currency); Foreign, $11.00. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A.

American Heart Journal

VOL. 23 MAY, 1942 NO. 5

Original Communications

THE GRAPHIC REGISTRATION OF THE NORMAL HEART SOUNDS

MAURICE B. RAPPAPORT, E.E., AND HOWARD B. SPRAGUE, M.D.
BOSTON, MASS.

A GRAPHIC ANALYSIS OF THE NORMAL HEART SOUNDS

IN A previous paper,[1] we discussed the acoustic principles involved in auscultation and the mechanisms that are effective in acoustic stethoscopes, electrical stethoscopes, and phonocardiographs. The discussion which follows is a continuation of this paper, and is intended to clarify the problems involved in auscultation and phonocardiography, with greater emphasis upon the clinical aspects.

Many relationships and phenomena exist in auscultation and phonocardiography which are not well understood. For example, it is evident from a review of the literature of the graphic registration of heart sounds that there are inconsistencies in the reported observations, relating chiefly to (1) The maximum and minimum duration of the normal heart sounds, (2) the intervals between certain of the normal heart sounds, (3) the intensity relationships of normal heart sounds, (4) the number of vibratory oscillations that compose the normal heart sounds, and (5) the frequency and pitch of the major components of normal heart sounds. It is the purpose of this study, therefore, to ascertain and analyze the causes for such divergences in phonocardiographic measurements and to attempt to arrive at more accurate evaluations.

We believe that these evaluations are necessary in order to explain the characteristics of auscultatory and phonocardiographic instruments and to place suitable limitations upon any single method of investigation.

ACOUSTIC CONSIDERATIONS

When a patient is auscultated with the usual stethoscope, the observer definitely does not hear the cardiac sound vibrations as they actually exist at the source because of three major forms of distortion, namely:

1. The heart sounds are modified in their path of travel from the source to the surface of the chest.

Received for publication Oct. 5, 1941.

2. The vibrations that reach the surface of the chest are further modified by the stethoscope and type of chest piece employed.

3. The human hearing mechanism (that is, the ear, the nervous pathways, and the brain) additionally modifies the heart sound vibrations.

The study of acoustics as related to auscultation, therefore, deals with the vibrations or disturbances set up in the chest and their transmission through the structures of the chest, as well as through the stethoscope, and with the resulting auditory perceptions.

Characteristics of the Chest in Sound Transmission.—Sound, which is the result of vibration of a medium, is capable of traveling through a solid, liquid, or a gas as a compressional wave, unless the medium is entirely inelastic. In other words, the ability of sound to travel through matter depends upon the elasticity, viscosity, and density of the medium. If the effects of viscosity are small, as is the case with water, air, metal, and bone, the sound energy may be transmitted with little loss. In some media, such as soft rubber or fatty breast tissue, the sound waves are almost immediately suppressed.

In a homogeneous substance, a sound wave will propagate itself at a velocity the magnitude of which depends upon the physical properties of the medium. The attenuation of the wave is governed by the viscosity and the spreading of the sound energy as the wave progresses. When sound energy travels from one medium into another of different physical properties, or when there is no longer homogeneity of the medium, transmissional losses in the form of refraction and reflection take place. Some media are capable of transmitting low frequency vibrations with less attenuation than high frequencies, and vice versa; this results in distortion of the sound.

There are many paths along which heart and chest sounds travel in the human body before they reach the surface. A considerable percentage of the sound energy never reaches the surface because of viscosity, elasticity, density, spreading, reflection, and refraction losses. Naturally, the intensity of the sound is maximum over the portion of the chest where the sound follows a path of minimum attenuation, and this location the physician normally selects with his stethoscope. Auscultatory experience has shown that murmurs produced by lesions of the four valves of the heart are heard with maximum intensity in certain areas of the chest, although there may be other sections of the chest surface which are closer to the valves under consideration.

The degree of modification to which heart sound vibrations are subjected as a result of transmissional losses is dependent upon the physical structure of the patient's chest. Transmissional losses in the average adult differ from those in a thin-chested child, an emaciated person, or an obese or barrel-chested subject.

Stethoscope Characteristics.—The stethoscope is a device which forms a closed acoustic system for conducting sounds by air transmission from the surface of the chest to the observer's ear. The experimental data obtained by Johnston and Kline[2] indicate that sound vibrations are altered by the acoustic stethoscope; we[1] have also demonstrated that every type of acoustic stethoscope modifies the sound vibrations in their passage from the chest wall to the ear.

The degree to which the heart sound vibrations are modified by the stethoscope depends to a considerable extent upon the type of chest piece employed. Our conclusions[1] on stethoscopic chest piece characteristics are:

"1. The open stethoscopic chest piece, or bell, when applied to the patient's chest, may be considered as a diaphragm type of chest piece. The skin which is bounded by the lip of the bell forms the diaphragm, and the fleshy portion under the skin acts as a damping medium.

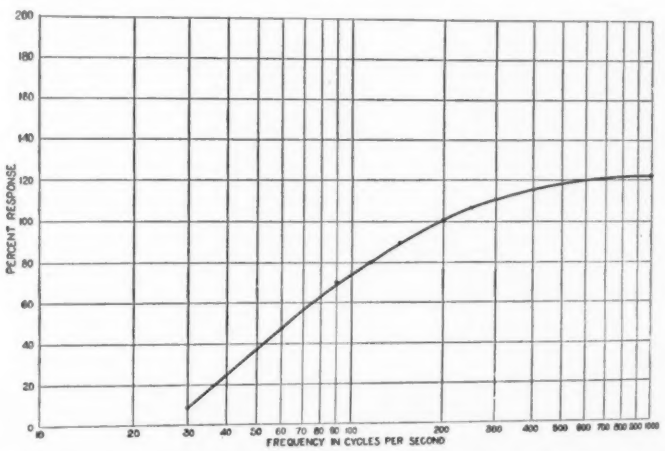


Fig. 1.—Frequency response characteristic of the average of a large number of acoustic stethoscopes, minus the effects of the chest piece. (After Rappaport and Sprague.[1])

"2. The larger the diameter of the open stethoscopic chest piece, the better its response to low-pitched sounds. This is accomplished at the expense of the higher frequency components.

"3. The greater the pressure with which the open stethoscopic chest piece is applied to the patient's chest, the better is the response of the stethoscope to higher frequency components. Thus, by varying the application pressure, the physician exerts a variable selective action upon the sounds because the natural period of the skin diaphragm which is bounded by the chest piece depends on the pressure with which it is applied.

"4. The principle of operation of the Bowles (diaphragm) chest piece is similar to that of the open bell, except that additional attenuation of

the lower pitched heart and chest sound components is accomplished by the action of the rigid diaphragm of the Bowles chest piece."

Fig. 1 shows the manner in which the average of a large number of stethoscopes modifies the heart sound vibrations with respect to frequency. This curve does not include the modifying effects of the stethoscopic chest pieces. The frequency response characteristic of any single acoustic stethoscope is not as regular as in Fig. 1 because all acoustic stethoscopes possess resonance peaks which superimpose themselves upon the smooth average curve.

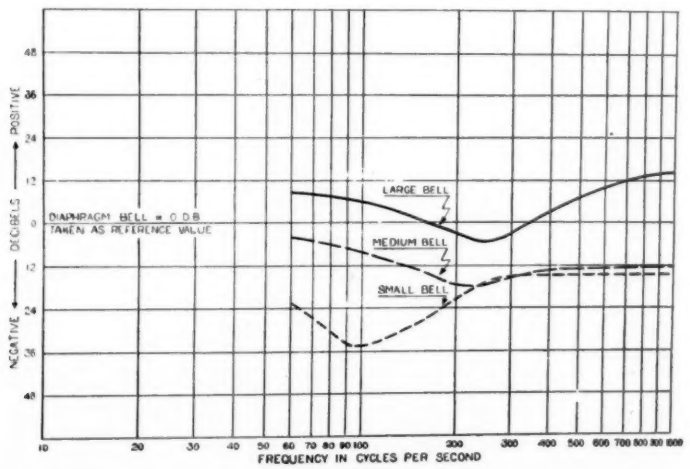


Fig. 2.—Resultant curves of the three open chest pieces of Fig. 3, as compared with diaphragm chest piece (Bowles). The higher the decibel reading, the higher the relative efficiency of the chest piece. (After Rappaport and Sprague.[1])

Fig. 3.—Photograph of three open and one "Bowles" diaphragm chest pieces represented in Fig. 2. The dimensions of the bells are as follows: The lip diameter of the large open bell is 2.0 inches; of the medium open bell, 1.5 inches; and of the small bell, 1.0 inch. The "Bowles" chest piece employs a diaphragm 0.015 inch thick and a freely working diameter of 1⅜ inches. The internal volume of the large bell is 12.7 c.c.; of the medium bell, 6.2 c.c.; of the small bell, 2.3 c.c.; and of the diaphragm bell, 2.5 c.c.

Fig. 2 shows the approximate relative efficiency of the four chest pieces of Fig. 3 with respect to frequency, as ascertained by us.[1] Some of the

more important conclusions that may be drawn from these curves are as follows:

"1. The efficiency of the three open bells improves, with respect to that of the diaphragm bell, as the frequency is decreased.

"2. The larger the diameter of the open bell, the more efficient is the bell at the lower frequencies.

"3. The large bell exhibits a resonance effect in the upper auscultatory region that is characteristic of a Helmholz resonator of such dimensions. The resonance points of the smaller bells are above the auscultatory range and therefore are not shown in the graph."

If a summation of the frequency response curves of the average acoustic stethoscope and any of the chest pieces is taken, the over-all frequency response curve may be ascertained. Obviously, as the resultant curve is not linear, the sounds must be altered before reaching the observer's ears.

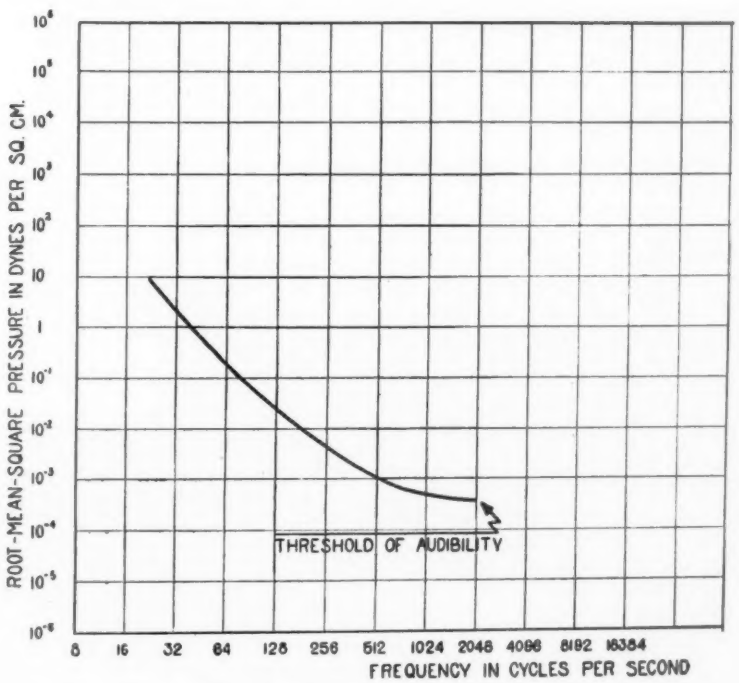


Fig. 4.—Average audiogram obtained from a large number of persons with normal hearing.

The Human Hearing Mechanism.—A characteristic of average normal hearing is the inability of the human ear to perceive as of equal loudness sounds of differing frequency which possess the same intensity. A graphic representation of this nonlinear characteristic of human hearing is known as an audiogram, and is obtainable by plotting as ordinates the minimum perceptible sounds applied to the tympanum of the ear

(expressed in dynes per square centimeter or bars), and as abscissae their frequency in cycles per second. Fig. 4 is an average audiogram (heart sound range) which was obtained on a large number of persons with normal hearing. The individual audiogram is not so smooth; peaks and valleys are superimposed. In addition, only rarely are two pairs of ears found to react alike, or even the two ears of any one person.

The curvature of the average normal audiogram approximates what is mathematically known as a logarithmic curve. *Thus, we may conclude that the human hearing mechanism alters or distorts logarithmically, with respect to frequency, the relative intensities of the components of the sounds that are transmitted to the tympanum of the ear by the stethoscope.*

The human hearing mechanism is capable of functioning over an enormous range of sound pressure or sound energy variations. For example, as shown in Fig. 4, at 20 cycles per second it takes about 10,000 times as much pressure to produce a "just perceptible" sound as it does at 512 cycles per second. A logarithmic representation of such enormous variations is shown in Fig. 4, and allows easier visualization.

PHONOCARDIOGRAPHY

Some knowledge of the presence of heart sounds and their value in cardiac diagnosis may date back to Hippocrates' work, *De Morbis,* in which vague reference to "immediate" auscultation is made. William Harvey, however, was one of the first to give convincing information about the presence of heart sounds *(De Motu Cordis).* It was not until 1819 that the character of heart sounds under normal and pathologic conditions was described by Laënnec,[3] who employed "mediate" auscultation in obtaining his data. Laënnec's observations were purely qualitative, as it was obviously impossible for him to make any positive measurements with his monaural stethoscope. His explanation of the mechanism of the heart sounds was incorrect because he attributed the first sound to ventricular contraction and the second to auricular contraction.

Hürthle,[4] in 1893, described a method of registering graphically the apex beat and the instant of occurrence of the first heart sound. The apparatus consisted of a microphone which excited an induction coil; this in turn excited a frog nerve-muscle preparation, which scratched a tracing on a smoked screen. In 1894, Einthoven and Geluk[5] substituted a capillary electrometer for Hürthle's frog nerve-muscle preparation and obtained the first graphic representation of the vibrations comprising the first heart sound. Some years later, Einthoven substituted the string galvanometer for the capillary electrometer, which decidedly increased the accuracy of the method.

Frank,[6, 7] in 1904, started a series of experiments with the object of devising a nonelectrical method for the graphic registration of the heart

sounds. He ultimately evolved what is known as the "Frank segment capsule," which has since proved useful in sphygmography as well as phonocardiography.

With the perfection of electronics, microphonic transducers, and galvanometric registering systems, improved electrical stethographs or phonocardiographs have come into use.

Normal Phonocardiographic Characteristics.—It is obviously impossible to control or standardize the transmissional properties of sound vibrations in chests of different persons. In phonocardiography, as well as stethoscopic auscultation, this variable must be tolerated. On the other hand, it is possible to control the operational characteristics of the phonocardiograph and stethoscope; they may be operated under standard conditions, provided suitable, universally accepted standards are selected. The characteristic of average normal hearing, as represented by the logarithmically shaped audiogram (Fig. 4), may also be considered as a constant. At the present time, there are no standard specifications for either the phonocardiograph or the stethoscope. This is certainly a deplorable situation when we consider that the stethoscope, especially, is one of the most widely used of medical instruments.

Throughout the literature, very little consideration has been given to the manner in which phonocardiographic measurements are related to the over-all frequency response of the phonocardiograph. In this study, three distinct types of phonocardiographic registration have been employed, namely, (1) linear, (2) stethoscopic, and (3) logarithmic. The resultant phonocardiograms have been compared.

The linear registration system possesses properties whereby sounds which are detected at the surface of the chest are not attenuated or accentuated with respect to frequency from practically zero cycles per second to above 1,000 cycles per second—the heart sound vibratory frequency band.[1] *Linear phonocardiography thus registers graphically the mechanical vibrations set up by cardiac action as they exist on the surface of the patient's chest—that is, the deviation of the recording galvanometer beam is proportional to the intensity of the vibration at the surface of the chest.* Obviously, in such a record, the large intensity, low frequency vibrations must be controlled by reducing the over-all sensitivity of the system, for their amplitude might be 10,000 times as great as that of the minimum recorded sounds. In such a system, therefore, high-pitched vibrations are often not recorded at all.

*The stethoscopic system of phonocardiographic registration[1] does not register the cardiac sound vibrations as they exist on the surface of the patient's chest, but as they are presented to the ears of an observer by an average acoustic stethoscope.** The over-all frequency response of

*By stethoscopic effect is meant the attenuation effects introduced at different frequencies by the stethoscope tubing and binaural ear pieces, but in each record there is the added effect of the chest piece used in the registration.

the stethoscopic system (Fig. 1) is not linear, but possesses a rising characteristic with respect to frequency increase over the heart sound frequency band—that is, the higher the pitch of the sound, the better it is transmitted.

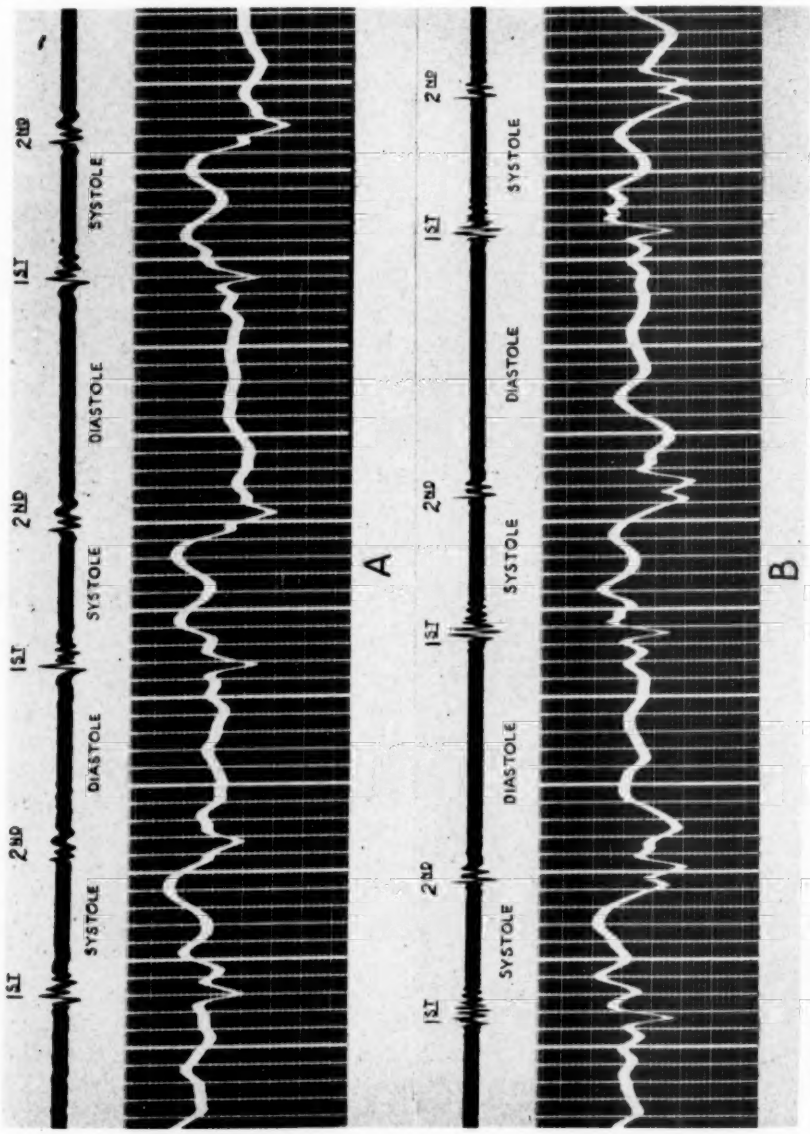
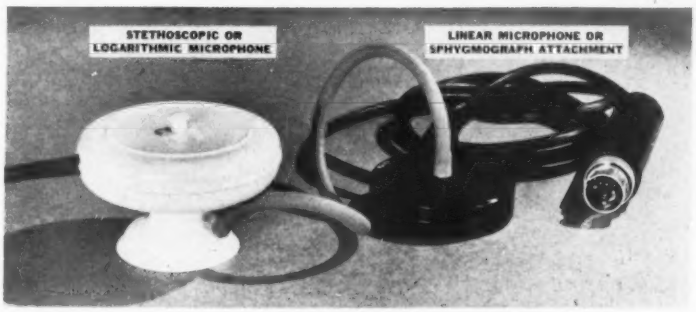


Fig. 5.—*A*, Simultaneous registration of stethoscopic (upper) and linear (lower) phonocardiograms on a normal person. *B*, Simultaneous registration of logarithmic (upper) and linear (lower) phonocardiograms on the same person as in *A*.

The logarithmic system[8] of phonocardiographic registration possesses an over-all frequency response equivalent to the summation of the curve of the average human audiogram (Fig. 4) and the curve of the average acoustic stethoscope (Fig. 1). The resultant logarithmic phonocardiogram is thus a graphic representation of the cardiac sound vibrations as

they are perceived by the average observer of normal hearing when an average acoustic stethoscope is employed.

The section on "Human hearing mechanism" will explain the use of the term "logarithmic" as employed here. The resulting graphic registration can be considered as a "human audiographic" record in which the amplitudes of the component sounds are registered in proportion to their relative loudness. That is, if the first heart sound, as heard, is twice as loud as the second heart sound, the amplitude of the graph of the first heart sound will be twice as great as that of the second heart sound.



A.

B.

Fig. 6.—*A*, Arrangement for the simultaneous registration of the linear and stethoscopic or linear and logarithmic phonocardiograms. *B*, Cross-section view of chest piece. The chest piece was the large bell shown in Fig. 3.

An understanding of this principle is fundamental to the interpretation of all phonocardiograms. Briefly, it indicates that "loudness" and "intensity" are different factors, and that "loudness" is an auditory perception determined by "intensity" and "frequency." If we attempt, therefore, to record what the ear terms "loudness," we must distort our simple linear record by introducing the peculiar logarithmic response of human hearing and the specific distortion of the acoustic stethoscope.

Let us now compare the phonocardiograms taken on a normal person at the apex with the linear, stethoscopic, and logarithmic registration systems. Fig. 5*A* shows a simultaneous registration of the stethoscopic (upper) and linear (lower) phonocardiograms. Fig. 5*B* shows a simultaneous registration of the logarithmic (upper) and linear (lower) phonocardiograms.

Fig. 6 is a photograph of the chest piece employed for the simultaneous registration of the linear and stethoscopic, or linear and logarithmic, phonocardiograms. This chest piece employs a double outlet to two distinct types of microphones, and thus permits simultaneous registration on the same area of the chest.

The linear phonocardiogram of Fig. 5*A* and *B* may readily be recognized as the registration of the "apex beat" or "cardiogram." Wiggers' explanation[25] of the mechanism of the apex beat is: "During ventricular contraction, all diameters of the heart decrease; the base is pulled downward and the large vessels stretched, but the apex does not move upward. Owing to the spiral arrangement of the muscle fasciculi, the heart rotates to the right with the result that more of the left ventricular surface has a frontal exposure. Such rotation particularly affects the apex, the forward motion pressing it more firmly against the chest wall. This gives rise to the pulsation in the fifth intercostal space referred to as the apex beat. Records of this pulsation called cardiograms represent only heart movement."

The literature on the cardiogram is sparse; practically all the present day knowledge of the subject may be found in the works of Wiggers,[25] Frank,[27] Weitz,[28] Frank and Hess,[29] Weber,[30] Krönecker,[31] and Crehore.[32] Wiggers[25] states: "Optical tracings of the apex beat have so far been shown of value in only one respect, namely, that they incorporate the heart sounds and so allow an exact establishment of systole and diastole. According to Weber, they enable us to determine the beginnings of auricular systole, ventricular systole, systolic ejection and the opening of the A-V valves, and are further particularly valuable in determining the isometric contraction phase. It is quite obvious, however, that the same temporal relations may be established as well by the use of the optical venous and arterial pulses. Whether any other significance may be attached to pathological tracings, further investigation alone can determine. Weitz, it is true, has published a large series of optically recorded cardiograms both from normal individuals and from those with cardiac lesions. Aside from the addition of a variety of murmur vibrations associated with the particular lesions in question and the greater predominance of positive waves, they show nothing that can be regarded as distinctive, in a diagnostic sense."

Taquini, Massell, and Walsh[33] have recently shown the usefulness of the cardiogram in the differentiation between the opening snap of the mitral valve and the third heart sound when the isometric relaxation phase of the left ventricle is shortened in the presence of mitral regurgitation. The authors claim: "Under such circumstances, the third sound, which is produced during rapid inflow into the left ventricle, might not show its usual relation to the 'v' wave of the venous pulse, for the latter is associated with pressure changes in the right ventricle. Therefore, in order to ascertain the nature of the extra sound in these

cases, it is necessary to take the phonocardiogram simultaneously with the records of the apical pulsation.''

The Auricular Sound.—By interrelating the linear, stethoscopic, and logarithmic phonocardiograms of Fig. 5*A* and *B*, we find that the cardiogram registers distinctly the auricular vibration or sound. The stethoscopic phonocardiogram shows a faint auricular vibration, and the logarithmic registration does not show any distinct vibrations which represent auricular contraction. In a considerable percentage of normal persons, the vibrational frequency of a transmitted auricular contraction is so low that it is incapable of passing through the average acoustic stethoscope. When such is the case, the stethoscopic phonocardiogram does not register the auricular sound. Human perception of such an auricular sound is an obvious impossibility with the added logarithmic attenuation. For the same reason, the logarithmic phonocardiogram will not register the auricular sound. The linear phonocardiogram is the only reliable phonocardiographic or auscultatory means of indicating the presence of a very low frequency auricular vibration. In phonocardiography, therefore, the cardiogram should prove useful as an indicator of the true location of the auricular contraction in the cardiac cycle.

The First Heart Sound.—In the apex cardiogram, the first heart sound is usually represented by a few coarse vibrations. The stethoscopic phonocardiogram on the same person shows somewhat similar, coarse vibrations, although attenuated, plus some superimposed, finer vibrations. The logarithmic phonocardiogram greatly attenuates the coarse vibrations and brings out a larger number of superimposed, finer vibrations.

Various investigators have shown that four factors are responsible for the production of the major vibrations which constitute the first heart sound. A discussion and bibliography on the subject may be found in the monograph by Orías and Braun-Menéndez.[34] The four factors are (1) the residual vibrations caused by auricular contraction—the auricular factor; (2) the muscular contraction and tension of the ventricular walls—the muscular factor; (3) the closure of the auriculoventricular valves—the valvular factor; and (4) the movements and distension caused by the ejection of blood from the ventricles into the arteries—the vascular factor; vibrations caused by opening of the semilunar valves initiate and fuse with this element of the first sound. In spite of conflicting experimental evidence, it appears likely that contraction of the ventricle produces vibrations in the absence of valve closure. These constitute the muscular factor and normally contribute to the early part of the first sound.

Caeiro and Orías[35] have indicated that it is possible to distinguish four distinct components in the phonocardiographic representation of a normal first heart sound. Our observations confirm those of Caeiro and

Orías. In Fig. 7, the four components may be distinguished in the stethoscopically registered phonocardiogram. The first component is a characteristically low frequency, or coarse, vibration which commences with the electrocardiographic QRS complex and normally precedes the apex of the wave. When an auricular sound is present, the first component usually merges with the auricular sound without a very definite interval. This phenomenon may be best seen in a linear phonocardiogram (Fig. 5*A*). The first component may thus be related to the auricular sound as a residual vibration, or the "auricular factor."

The vibrations which comprise the second component may be distinguished from the vibrations of the first component by their characteristically higher frequency and larger amplitude in a stethoscopically registered phonocardiogram. The second component always commences after the apex of the electrocardiographic QRS complex, and represents the beginning of the isometric, or presphygmic, phase of ventricular contraction. The second component records the closure of the mitral and tricuspid valves.

The third component is usually distinguishable from the second component (although it is of somewhat similar appearance) by a separation or slight splitting effect. The third component is synchronous with the opening of the semilunar valves and the onset of ventricular ejection.

The fourth component is composed of coarse vibrations which may extend to the peak of the "c" wave of the phlebogram or the anacrotic notch of a simultaneously registered central arterial pulse. Quite often the fourth phase vibrations terminate prior to, but rarely after, the peak of the "c" wave in a normal person. The vibrations which compose the fourth phase are thus believed to be caused by the acceleration of the blood in the arteries during the maximum ejection phase of ventricular systole.

In the linear phonocardiogram, there are always a preponderance of low frequency vibrations and a total or almost total lack of any of the higher frequency components that are so obviously registered in the stethoscopic and logarithmic phonocardiograms. A harmonic analysis of the frequency components of the first heart sound, which is a conglomeration of unrelated frequencies, shows that the coarse, or low frequency, vibrations are much greater in intensity than the higher frequency components. *The amplitude ratio of the major coarse and fine vibrations is so large that, when registered linearly, the fine vibrations are entirely lost or are, at best, insignificant. Thus, the linear phonocardiogram is extremely efficient in the registration of the first and fourth phases of the first heart sound and decidedly inefficient as an indicator of the second and third phases.*

The stethoscopic phonocardiogram attenuates the first and fourth phases and brings out distinctly the higher frequency second and third components. The reason the second and third components appear to be

of such magnitude in this type of registration is that more amplification is employed than is permissible in linear phonocardiography. If an equal amount of amplification were employed in linear phonocardiography, with the object of bringing out the second and third components, the deflections of the first and fourth components would be so large as to mask the second and third components. *It so happens that, with stethoscopic registration plus the additional amplification, the attenuation effects upon the first and fourth components are insufficient for obliteration, and sufficient to bring out clearly the second and third components.*

Although the average acoustic stethoscope is capable of conducting the selectively attenuated four components of the first heart sound to the tympana of the ears, the observer is capable of hearing merely the higher frequency second and third components, and very little or practically none of the first and fourth components. The reason human perception is so inefficient in the detection of the first and fourth components is that logarithmic hearing adds a still greater degree of selective attenuation. An interesting fact is that, at times, evidence of a first and fourth component may be present in the logarithmic phonocardiogram, but the observer, although extremely competent, will not hear the lower frequency vibrations because of the masking effects[1] of the apparently more intense second and third components upon the first and fourth.

Simultaneous registration of the stethoscopic or logarithmic phonocardiogram with the venous pulse may serve as a means of differentiating between a prolonged first heart sound and a first heart sound followed by a short systolic murmur. None of the four components of the first heart sound normally has a duration which allows it to extend beyond the peak of the venous pulse "c" wave. *Thus, it is reasonably safe to say that vibrations which extend beyond the peak of the "c" wave are the components of a systolic murmur.* On rare occasions, an extremely low frequency vibration may occur just after the peak of the "c" wave (during reduced ventricular ejection). Also, the fourth component vibrations are of a characteristically lower frequency than those of a systolic murmur, which also aids in the differentiation, even though the systolic murmur may commence early in the first heart sound, but not before the isometric contraction phase, i.e., the second component.

It should be of interest at this point to mention that a linear phonocardiograph is essentially an electrical sphygmograph.[1, 59] All the sphygmograms considered in this study were registered electrically or in accordance with linear phonocardiographic technique. Electrical sphygmography[1] possesses a number of inherent advantageous characteristics not readily obtainable with optical systems which employ the "Frank segment capsule" or any of its known modifications. A few of the more important characteristics are critical damping, high speed of response with ample sensitivity, good photographic definition because

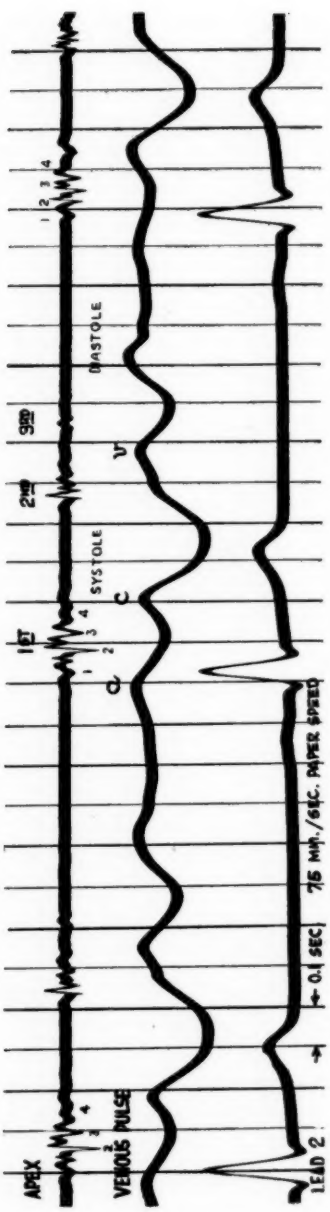


Fig. 7.—Simultaneous stethoscopic phonocardiogram, venous pulse, and electrocardiogram, to illustrate the relationship of the four components of the first heart sound.

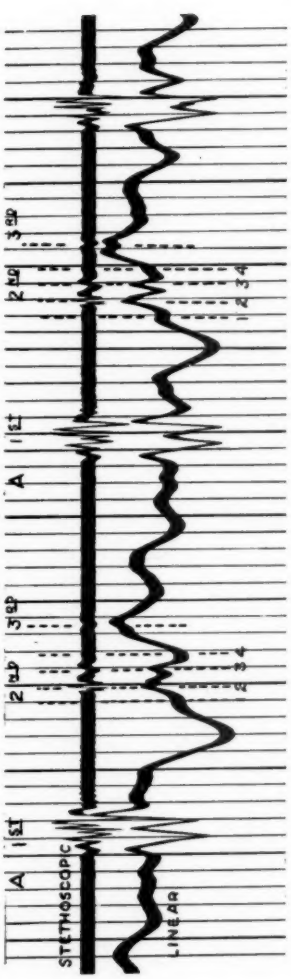


Fig. 8.—Simultaneous stethoscopic (upper) and linear (lower) phonocardiogram at the apex of a normal person. The four components of the second heart sound are present in the stethoscopic phonocardiogram, and their phase relationship to the apex beat is shown. A slight auricular vibration and the first and third heart sounds are distinctly registered.

of low optical magnification, simplicity of operation, automatic centering of the recording beam, adjustable sensitivity control, and nondeteriorating components. An important characteristic of the electrical sphygmograph attachment is that it may be used in an electrocardiographic channel (electronic type), and thus permits the registration of either an electrocardiographic lead or a sphygmogram.

Kountz, Gilson, Smith, and Edwards[60-62] have recently published "vibrograms" of the heart sounds with an apparatus which had a "drop off in transmission of less than 2 per cent between five cycles and fifteen hundred cycles per second." The authors give no figures for frequency response below five cycles per second. If the over-all response is linear from practically zero cycles per second, the apparatus is equivalent to our linear phonocardiograph and may be classified as a good sphygmograph. If the vibrograph response drops sharply below five cycles per second, it is no longer an accurate sphygmograph, but may be classified as a phonocardiograph which is linear between five cycles and 1,500 cycles per second.

The Second Heart Sound.—Billing,[36] in 1832, suggested that the second sound may be attributed to the closure of the semilunar valves. Rouanet,[37] in the same year, set up an experiment and verified Billing's theory. In 1882, Webster[38] suggested that additional sound vibrations may occur during this phase of the cardiac cycle as a result of arterial wall and blood column vibrations. The consensus at the present time favors these investigators.

Graphic analysis of a large number of phonocardiograms shows that the composite, normal, second heart sound, as recorded at the apex, is composed of four distinct components. The reason a composite of a large number of normal graphic registrations of the second heart sound is referred to in this analysis is that all four components do not always register distinctly in a single phonocardiogram. Fig. 8 shows a simultaneous stethoscopic (upper) and linear (lower) phonocardiogram, registered at the apex, in which the four components may be detected. In Fig. 9 there are additional records which show the four components of the second heart sound.

A composite linear phonocardiogram shows that the second heart sound commences with a small, subaudible vibration which we shall call the first component. The first component is quite distinct in the linear phonocardiogram of Fig. 8. This initial vibration is immediately followed by a few coarse vibrations—the second component. In Fig. 8 the second component is represented by a large, notched vibration. The second component is, in turn, followed by one or more very coarse vibrations which are usually of smaller intensity than those of the second component. In Fig. 8 the third component is represented by a single vibration. At the end of the third component, and simultaneous with the apex of the "v" wave of a venous pulse registration, a coarse vibra-

tion, or negative peak, terminates the second heart sound—the fourth component. In Fig. 8 the fourth component is represented by a notched, negative dip.

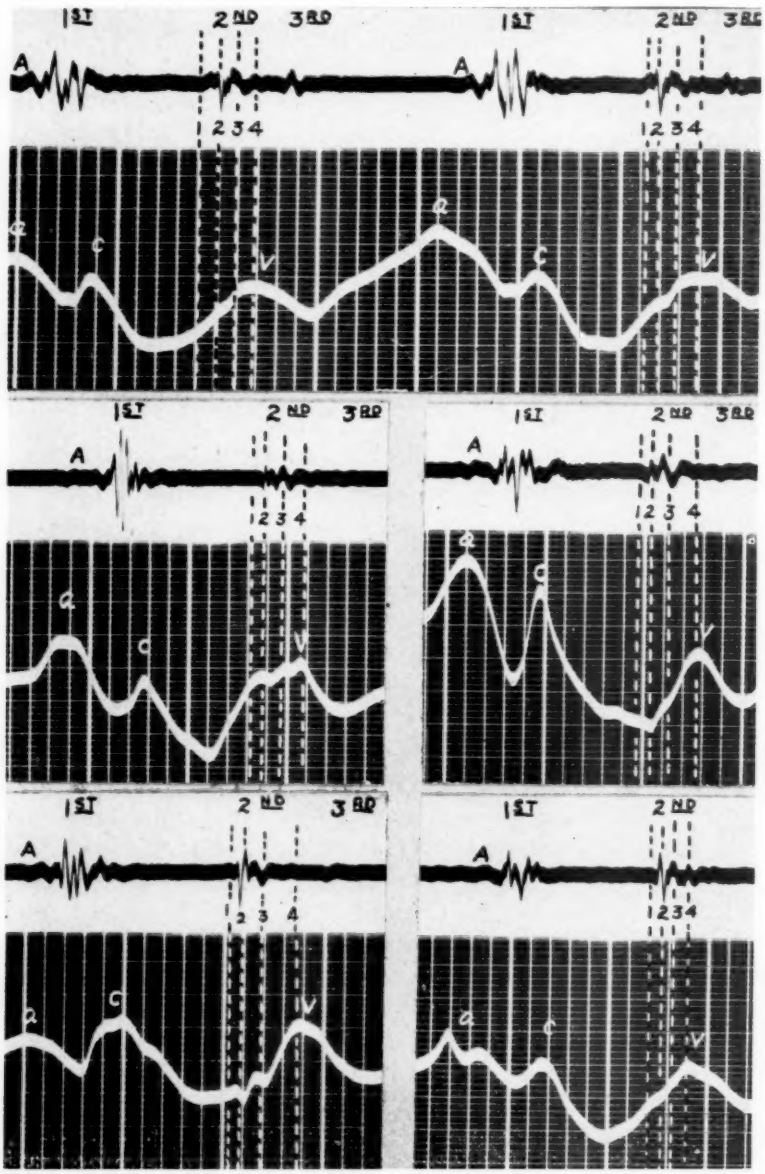


Fig. 9.—Simultaneous stethoscopic phonocardiograms at apex (upper) and phlebograms (lower) of five normal persons, showing the four components of the second heart sound and their relationship to the phlebogram. The auricular, first, and third heart sounds are also distinctly registered.

A composite, normal, stethoscopic phonocardiogram shows the first component of the second heart sound, but with some attenuation; this is well represented in Fig. 8. The first component is more distinct in some

of the records of Fig. 9. The second component is present, with the addition of superimposed higher frequency components; this is excellently illustrated by Fig. 8. The third component is present, but attenuated; Fig. 8 shows the third component distinctly. The fourth component is frequently present in a stethoscopic phonocardiogram, but considerably attenuated. In Fig. 8 a small wavelet representing the fourth component is noticeable.

A composite logarithmic phonocardiogram shows evidence of the presence of a first component of the second heart sound. The second component is present with more superimposed higher frequency components than appear in the composite stethoscopic phonocardiogram. The third and fourth components are usually completely eliminated.

The beginning of the second heart sound, or the first component, occurs at the beginning of the relaxation and diastolic fall of pressure in the ventricle. The second component vibrations may be ascribed to the closure of the semilunar valves. The vibrations that compose the second component contain many frequencies, in which the lowest predominate. This accounts for the introduction of higher frequency components in the stethoscopic phonocardiogram and still higher components in the logarithmic phonocardiogram at the expense of the lower frequency vibrations.

The third component of the second heart sound is probably caused by arterial wall and blood column vibrations. An additional source of vibration in this region may be the natural period vibration of the chest wall, which may be set into oscillation by the vibrations of the second component.

The fourth component vibration is the result of the opening of the mitral and tricuspid valves, as it always occurs simultaneously with the apex of the venous pulse "v" wave. The common occurrence of the fourth component in a considerable percentage of linear and stethoscopic phonocardiograms from normal persons, and its total absence in logarithmic phonocardiograms, indicate that the so-called "opening snap" is present in normal persons at a subaudible level. *Only in mitral stenosis does the fourth component become audible.*

In every normal phonocardiogram the train of vibrations which compose the four components of the second heart sound terminates with, or prior to, the occurrence of the simultaneously registered venous pulse "v" wave. Thus, a simultaneous phonocardiogram and phlebogram should supply sufficient data for the differentiation between a prolonged second heart sound and a second heart sound followed by a short diastolic murmur. *In other words, any vibrations which continue beyond the apex of the simultaneously registered venous pulse "v" wave are components of a diastolic murmur. This, of course, excludes the vibrations that may set up a third heart sound.*

The Third Heart Sound.—The generally accepted explanation of the cause of the third heart sound is well summed up by Orías and Braun-

Menéndez[34]: "The third heart sound is caused by vibrations of the ventricular walls due to their sudden distension by the inrush of blood from the auricles in the first moments of rapid ventricular filling." This third heart sound hypothesis, according to Orías and Braun-Menéndez, was first proposed by Ohm,[39] in 1921, and has been supported by Frey,[40] Lian,[41, 42] Gübergritz,[43] Melik-Gülnasarian,[44] Leonhardt,[45] Schütz,[46] and Braun-Menéndez and Orías.[47] Orías and Braun-Menéndez further state: "By the term 'ventricular walls' no distinction is implied between muscular and tendinous structures or valves. Furthermore, though this cause is stressed as the principal one, other subsidiary factors are not necessarily excluded. Some authors (Melik-Gülnasarian[44] and Routier and Van Bogaert[48]) stress the importance of an increased cardiac distensibility (diminution of tone) due to vagotonic disturbances in favouring the production of the sound."

Almost every linear phonocardiogram shows some evidence of a low frequency vibration which starts during the downslope of the simultaneously registered venous pulse "v" wave. In some normal persons a single positive vibration may be present, and, in others, two or possibly three such vibrations appear, but are of lesser intensity. The stethoscopic phonocardiogram usually shows the third heart sound as a single oscillation, but not so frequently or distinctly as does the linear phonocardiogram. The logarithmic phonocardiogram likewise registers a normal third heart sound as a single oscillation. Registration of a normal third heart sound is decidedly less frequent in a logarithmic phonocardiogram.

DURATION OF NORMAL HEART SOUNDS

The First Heart Sound.—Table I is a compilation of data found in the literature pertaining to the duration of the first heart sound in normal persons. The minimum normal duration of the first heart sound, as observed by Roos, is 0.041 second; whereas Strähl claims that it is 0.125 second—approximately a 3 to 1 ratio. Einthoven's measurement for maximum normal duration is 0.176 second; whereas Roos's is 0.064 second—a 2.75 to 1 ratio.

Differences in maximum and minimum measurements cannot be wholly attributed to the phonocardiographic method employed, such as direct versus electrical. As shown in Table I, among the authors who employed the direct method, Wiggers (0.05 sec.) and Strähl (0.125 sec.) showed the largest difference for minimum duration of the first heart sound—a 2.5 to 1 ratio. The largest difference for maximum duration of the first heart sound is between Strähl (0.175 sec.) and Ohm (0.097 sec.)—a 1.8 to 1 ratio.

Similar differences in measurement are found to exist among the investigators who employed the electrical phonocardiographic method. Einthoven obtained a minimum duration for the first heart sound of

0.058 second; whereas Kahn observed a minimum duration of 0.095 second—a ratio of 1.64 to 1. Einthoven obtained a maximum duration of 0.176 second; whereas Kahn's measurement was 0.109 second—a ratio of 1.62 to 1.

A comparison of the data obtained with Einthoven's electrical method and Wiggers' direct method indicates that they are in agreement within a reasonable percentage as to maximum and minimum duration.

TABLE I

COMPILATION OF DATA FOUND IN THE LITERATURE PERTAINING TO THE DURATION OF THE FIRST HEART SOUND IN NORMAL PERSONS

AUTHOR	YEAR OF OBSERVATION	DURATION OF FIRST SOUND IN SECONDS	METHOD
Einthoven, W.[9]	1907	0.058-0.176	Electrical
Roos, E.[10]	1908	0.041-0.064	Flame
Weiss, O.[11]	1909	0.068	Direct
Gerhartz, H.[12]	1911	0.11	Direct
Kahn, R. H.[13]	1911	0.095-0.109	Electrical
Lilienstein[14]	1911	0.08	Electrical
Ohm, R.[15]	1912	0.083-0.097	Direct
Eyster, W.[16]	1911	0.128	Electrical
Kapff[17]	1914	0.079-0.116	Direct
Bridgman, E. W.[18]	1915	0.145	Electrical
Strähl, E. O.[19]	1920	0.125-0.175	Direct
Kanner, L.[20]	1921	0.16	Direct
Wiggers, C. J.[21]	1923	0.05-0.152	Direct
Schütz, E.[22]	1933	0.09-0.12	Electronic
Orías, O.[23]	1936	0.10-0.17	Direct
Segura, A. S.[24]	1937	0.10-0.14	Direct

For analysis, we selected thirty-three normal, male, university students and made the following registrations at the apex with the subject in a supine position:

1. Stethoscopic phonocardiogram simultaneous with electrocardiographic Lead II.
2. Stethoscopic phonocardiogram simultaneous with the phlebogram.
3. Logarithmic phonocardiogram simultaneous with electrocardiographic Lead II.
4. Logarithmic phonocardiogram simultaneous with the phlebogram.

Table II shows our measurements of the duration of the first heart sound in the thirty-three normal persons. *The maximum duration of the first heart sound by the stethoscopic registration method was 0.165 second, as compared to 0.135 second by the logarithmic method. The minimum duration by the stethoscopic method was 0.105 second, and, by the logarithmic method, it was 0.08 second.*

In every one of the thirty-three normal persons listed in Table II, the first heart sound was of longer duration in the stethoscopic phonocardiogram than it was in the logarithmic phonocardiogram. This difference in duration is due to the greater amount of attenuation that the first

and fourth components are subjected to by the logarithmic registration system. We believe that herein lies the explanation for the divergent data of Table I. *In other words, lack of agreement as to the duration of the first heart sound is due primarily to dissimilar frequency response characteristics inherent in the phonocardiographs employed by the investigators.*

TABLE II

DURATION OF THE FIRST HEART SOUND IN THIRTY-THREE NORMAL PERSONS, MEASURED IN STETHOSCOPIC AND LOGARITHMIC PHONOCARDIOGRAMS

SUBJECT NUMBER	AGE (YEARS)	DURATION OF FIRST SOUND (SECONDS)	
		STETHOSCOPIC	LOGARITHMIC
1	24	0.160	0.120
2	24	0.120	0.090
3	28	0.120	0.090
4	22	0.135	0.120
5	21	0.125	0.105
6	22	0.140	0.120
7	19	0.130	0.100
8	21	0.160	0.115
9	20	0.145	0.125
10	26	0.105	0.080
11	23	0.155	0.125
12	24	0.105	0.100
13	22	0.140	0.115
14	22	0.120	0.110
15	21	0.150	0.115
16	22	0.110	0.095
17	22	0.115	0.080
18	21	0.110	0.085
19	21	0.110	0.090
20	22	0.150	0.135
21	21	0.120	0.090
22	20	0.115	0.095
23	23	0.125	0.100
24	22	0.165	0.105
25	22	0.150	0.120
26	21	0.130	0.105
27	22	0.120	0.110
28	22	0.140	0.085
29	19	0.110	0.100
30	23	0.110	0.095
31	21	0.115	0.105
32	38	0.115	0.085
33	36	0.120	0.085

We have shown that various types of chest pieces modify the frequency response of the phonocardiograph. The phonocardiograms summarized in Table II were registered with the 5-cm. diameter chest piece of Fig. 3. The reason such a large chest piece was employed is that it is highly efficient in the low frequency region where the normal heart sounds lie. Also, the application pressure[1] with such a chest piece is not critical. That is, the smaller the diameter of the chest piece, the more critical does the application pressure to the patient's chest become with respect to low frequency attenuation.

Smaller diameter chest pieces, and certainly the Bowles diaphragm types, attenuate the first and fourth components to a greater extent than

does the large, 5 cm. bell. It is thus obvious that more portions of the first and fourth components are lost in the phonocardiogram as the chest piece is decreased in diameter. The diaphragm chest piece attenuates these heart sound components most. In ascertaining the duration of the first heart sound, the investigators listed in Table I gave practically no consideration to this important characteristic.

The following are the factors, therefore, which may affect the duration of the first heart sound as detected at the surface of the chest: (1) Attenuation effects by the chest structure, (2) the frequency response characteristic of the phonocardiograph, and (3) the type of chest piece employed. (If small diameter chest pieces are used, the application pressure is an additional modifying factor.)

A number of investigators[9, 11, 12, 14, 17-24] have published figures on the frequency in cycles per second and the number of vibrations that compose the first heart sound. In our opinion, such figures are misleading and have very little meaning. For example, it has been shown that the four elements of the first heart sound have dissimilar frequency components. Under such conditions, how can such a complex train of waves be expressed with any accuracy by a single frequency value? Furthermore, the vibrational frequencies and the number of vibrations which compose the first heart sound are dependent upon the frequency response of the phonocardiograph and the type of chest piece employed. *To conclude, the first heart sound is a noise consisting of a conglomeration of unrelated frequencies that cannot be accurately regarded as a pure harmonic vibration, which many investigators have attempted to do.*

The Second Heart Sound.—Table III is a compilation of data by various authors on the duration of the normal second heart sound. The duration measurements of the second heart sound are as divergent as those published on the first heart sound.

Our measurements for the duration of the second heart sound in the thirty-three normal persons are given in Table IV. These measurements were made on the same stethoscopic and logarithmic phonocardiograms from which Table II was derived. *The maximum duration of the second heart sound by the stethoscopic registration method was 0.145 second, as compared to 0.110 second by the logarithmic method. The minimum duration by the stethoscopic method was 0.085 second, and, by the logarithmic method, 0.08 second.*

The data of Table IV again illustrate how the first, third, and fourth components of the second heart sound are more effectively attenuated in the logarithmic than in the stethoscopic phonocardiograms in such a way as to alter the measurable duration. Likewise, phonocardiographic data obtained with apparatus of dissimilar characteristics cannot be expected to correspond, as was true for the first heart sound.

The second heart sound consists of a conglomeration of unrelated frequencies, as does the first heart sound. Therefore, the statement which

TABLE III

COMPILATION OF DATA FOUND IN THE LITERATURE PERTAINING TO THE DURATION OF THE SECOND HEART SOUND IN NORMAL PERSONS

AUTHOR	YEAR OF OBSERVATION	DURATION OF SECOND SOUND (SECONDS)	METHOD
Einthoven, W.[9]	1907	0.041-0.104	Electrical
Roos, E.[10]	1908	0.045-0.048	Flame
Weiss, O.[49]	1910	0.071	Direct
Gerhartz, H.[12]	1911	0.07	Direct
Kahn, R. H.[13]	1911	0.068-0.081	Electrical
Lilienstein[14]	1911	0.06	Electrical
Ohm, R.[15]	1912	0.052-0.061	Direct
Eyster, J. A. E.[16]	1912	0.095	Electrical
Kapff[17]	1914	0.043-0.093	Direct
Bridgman, E. W.[18]	1915	0.089	Electrical
Strähl, E. O.[19]	1920	0.062-0.10	Direct
Kanner, L.[20]	1921	0.10	Direct
Frey, W.[50]	1926	0.062-0.10	Electrical
Yoshioka, J.[51, 52]	1932	0.095-0.19	Electrical
Braun-Menéndez, E., and Orías, O.[53]	1934	0.10-0.14	Direct

TABLE IV

DURATION OF THE SECOND HEART SOUND IN THIRTY-THREE NORMAL PERSONS, MEASURED IN STETHOSCOPIC AND LOGARITHMIC PHONOCARDIOGRAMS

SUBJECT NUMBER	AGE (YEARS)	DURATION OF SECOND SOUND (SECONDS)	
		STETHOSCOPIC	LOGARITHMIC
1	24	0.135	0.105
2	24	0.135	0.090
3	28	0.130	0.065
4	22	0.125	0.090
5	21	0.125	0.100
6	22	0.140	0.105
7	19	0.145	0.080
8	21	0.120	0.085
9	20	0.130	0.070
10	26	0.135	0.075
11	23	0.130	0.080
12	24	0.125	0.070
13	22	0.120	0.080
14	22	0.110	0.085
15	21	0.130	0.110
16	22	0.100	0.060
17	22	0.100	0.070
18	21	0.105	0.090
19	21	0.095	0.075
20	22	0.135	0.095
21	21	0.110	0.090
22	20	0.125	0.085
23	23	0.105	0.065
24	22	0.130	0.110
25	22	0.125	0.075
26	21	0.115	0.085
27	22	0.120	0.100
28	22	0.125	0.065
29	19	0.130	0.110
30	23	0.095	0.070
31	21	0.140	0.105
32	38	0.115	0.060
33	36	0.085	0.055

we made with regard to measurements on the frequency in cycles per second and the number of component vibrations holds just as true for the second sound as it does for the first.

The Third Heart Sound.—The duration of the third heart sound was measured in the thirty-three normal stethoscopic and logarithmic phonocardiograms (Table V). The measurements in several of the normal curves are approximate because of the difficulty of accurately judging the start and end point of such a typically coarse vibration of low amplitude. *The maximum duration by the stethoscopic method was 0.085 second; and by the logarithmic method, 0.05 second. The minimum stethoscopic duration was 0.03 second, and the logarithmic minimum was 0.015 second.*

TABLE V

DURATION OF THE THIRD HEART SOUND IN THIRTY-THREE NORMAL PERSONS, MEASURED IN STETHOSCOPIC AND LOGARITHMIC PHONOCARDIOGRAMS

SUBJECT NUMBER	AGE (YEARS)	DURATION OF THIRD SOUND (SECONDS)	
		STETHOSCOPIC	LOGARITHMIC
1	24	0.085	0.035
2	24	0.080	0.020
3	28	0.050	Not present
4	22	0.055	Not present
5	21	0.050	0.050
6	22	0.070	Not present
7	19	0.055	Not present
8	21	0.050	Not present
9	20	0.080	0.025
10	26	0.060	Not present
11	23	0.030	0.015
12	24	0.045	Not present
13	22	0.050	Not present
14	22	0.065	0.015
15	21	Not present	Not present
16	22	Not present	Not present
17	22	0.060	Not present
18	21	0.040	0.035
19	21	0.035	Not present
20	22	0.055	0.030
21	21	Not present	Not present
22	20	0.040	Not present
23	23	Not present	Not present
24	22	0.065	0.030
25	22	Not present	Not present
26	21	0.050	Not present
27	22	0.040	Not present
28	22	0.060	0.045
29	19	0.055	Not present
30	23	0.060	Not present
31	21	0.055	Not present
32	38	0.035	Not present
33	36	Not present	Not present

The third heart sound registered clearly in twenty-seven of the thirty-three stethoscopic phonocardiograms (85 per cent); whereas the logarithmic phonocardiograms showed a distinct third sound in ten of the normal persons (30 per cent).

TABLE VI

INTERVAL BETWEEN THE BEGINNING OF THE SECOND HEART SOUND AND THE CENTER OF THE THIRD HEART SOUND IN THIRTY-THREE NORMAL PERSONS, MEASURED IN STETHOSCOPIC AND LOGARITHMIC PHONOCARDIOGRAMS

(There is no correlation between these intervals and the heart rate.)

SUBJECT NUMBER	AGE (YEARS)	STETHOSCOPIC INTERVAL BETWEEN SECOND AND THIRD SOUNDS (SECONDS)	LOGARITHMIC INTERVAL BETWEEN SECOND AND THIRD SOUNDS (SECONDS)	HEART RATE PER MINUTE
1	24	0.185	0.175	69
2	24	0.180	0.160	78
3	28	0.185	Not present	75
4	22	0.190	Not present	60
5	21	0.175	0.165	75
6	22	0.205	Not present	60
7	19	0.190	Not present	68
8	21	0.190	Not present	54
9	20	0.190	0.165	57
10	26	0.180	Not present	72
11	23	0.180	0.175	66
12	24	0.160	Not present	84
13	22	0.160	Not present	68
14	22	0.185	0.165	63
15	21	Not present	Not present	66
16	22	Not present	Not present	81
17	22	0.160	Not present	72
18	21	0.170	0.160	72
19	21	0.160	Not present	66
20	22	0.200	0.185	63
21	21	Not present	Not present	78
22	20	0.200	Not present	75
23	23	Not present	Not present	93
24	22	0.195	0.170	63
25	22	Not present	Not present	66
26	21	0.185	Not present	72
27	22	0.165	Not present	66
28	22	0.180	0.160	78
29	19	0.175	Not present	75
30	23	0.185	Not present	69
31	21	0.195	Not present	57
32	38	0.240	Not present	96
33	36	Not present	Not present	84

Table VI gives the intervals between the beginning of the second heart sound and the midpoint of the third sound. The midpoint of the third sound was selected as a reference because it may be estimated with greater ease than the starting point. *The stethoscopic method showed a maximum interval of 0.240 second and a minimum of 0.160 second. The maximum logarithmic interval was 0.185 second, and the minimum, 0.160 second.* The interval difference between stethoscopic and logarithmic methods may be accounted for by the obliteration or attenuation of the first component of the second heart sound, which effectively shortens the interval. Obviously, phonocardiographs of dissimilar frequency response will not supply similar data. This is well illustrated by the values in Table VII.

Miscellaneous Relationships.—The amplitude ratio of the first to the second heart sound in the thirty-three normal apex phonocardiograms

TABLE VII

COMPILATION OF DATA FROM THE LITERATURE PERTAINING TO THE INTERVAL BETWEEN THE SECOND AND THIRD HEART SOUNDS

AUTHOR	YEAR OF OBSERVATION	INTERVAL BETWEEN SECOND AND THIRD SOUNDS (SECONDS)	METHOD
Einthoven, W.[9]	1907	0.13	Electrical
Lewis, T.[54, 55]	1913	0.18	Electrical
Hess, O.[56]	1915	0.26	Direct
Bridgman, E. W.[18]	1915	0.13-0.18	Electrical
Leonhardt, W.[45]	1932	0.115-0.15	Electrical
Clerc, A., Zodac-Kahn, B., and Tavecchi, G.[57]	1934	0.12-0.18	Electrical
Braun-Menéndez, E., and Orías, O.[53]	1934	0.11-0.14	Direct
Duchosal, P.[58]	1935	0.11-0.18	Electrical

TABLE VIII

AMPLITUDE RATIO OF FIRST HEART SOUND DIVIDED BY SECOND HEART SOUND IN THIRTY-THREE NORMAL STETHOSCOPIC AND LOGARITHMIC PHONOCARDIOGRAMS

SUBJECT NUMBER	AGE (YEARS)	STETHOSCOPIC AMPLITUDE (RATIO OF FIRST SOUND DIVIDED BY SECOND SOUND)	LOGARITHMIC AMPLITUDE (RATIO OF FIRST SOUND DIVIDED BY SECOND SOUND)
1	24	1.30	0.93
2	24	1.43	1.10
3	28	1.43	1.16
4	22	1.45	1.00
5	21	0.92	1.00
6	22	1.00	1.06
7	19	1.20	0.67
8	21	0.71	1.00
9	20	1.04	0.92
10	26	1.27	1.27
11	23	0.78	0.84
12	24	1.00	0.68
13	22	0.85	0.75
14	22	1.44	0.92
15	21	0.83	0.70
16	22	0.90	0.62
17	22	1.00	0.75
18	21	0.94	1.11
19	21	0.66	0.75
20	22	1.00	2.00
21	21	0.93	0.77
22	20	0.67	0.59
23	23	1.00	1.13
24	22	1.11	0.88
25	22	1.07	1.00
26	21	0.91	0.91
27	22	1.04	1.43
28	22	1.18	1.19
29	19	1.20	1.20
30	23	1.00	0.54
31	21	0.72	0.73
32	38	1.00	1.09
33	36	0.71	0.64

is listed in Table VIII. *In twenty of the thirty-three normal stethoscopic phonocardiograms (60 per cent) the amplitude of the first heart sound was greater than, or equal to, that of the second sound. Fifteen of the logarithmic phonocardiograms (45 per cent) showed that the amplitude of the first sound was greater than, or equal to, that of the second.* This difference between stethoscopic and logarithmic registration may be explained by the greater preponderance of higher frequency components in the second sound than in the first. The relationship does not necessarily hold true for older persons.

In nineteen of the thirty-three stethoscopic phonocardiograms (58 per cent), a slight trace of systolic murmur was present. The logarithmic registrations showed some evidence of a systolic murmur in twenty-eight of the thirty-three subjects (85 per cent). Furthermore, the logarithmic system registered the murmur whenever the stethoscopic system did. This indicates that the selective attenuating properties which are peculiar to human hearing tend to bring out a slight murmur more efficiently because of the greater preponderance of high frequency components in such a murmur.

The auricular sound was present in twenty-nine of the thirty-three stethoscopic phonocardiograms (88 per cent); whereas the logarithmic system registered it in seven of the thirty-three subjects (21 per cent). This illustrates that human hearing is relatively inefficient in the detection of normal auricular sounds because of their low vibratory frequency.

SUMMARY AND CONCLUSIONS

1. When a patient is auscultated in the usual stethoscopic manner, the observer does not hear the cardiac vibrations as they actually exist at the source because of three major forms of modification, namely:

a. The heart sounds are altered in their transmission from the source to the surface of the chest.

b. The heart sounds that reach the surface of the chest are additionally modified by the acoustic stethoscope and the type of chest piece employed.

c. The observer does not perceive the heart sound vibrations as they are transmitted to the ears by the acoustic stethoscope.

2. The three major forms of cardiac sound modification are related to auscultation as follows:

a. The chest transmissional factor must be considered and handled as a variable quantity.

b. Modification effects that are introduced by acoustic stethoscopes and their chest pieces may be made nonvariable. No attempts at stethoscopic standardization have as yet been made. Until such standardizations are accomplished, the stethoscopic factor must be considered as a variable quantity in auscultation.

c. Modification effects that are introduced by average normal hearing may be considered as a constant quantity in auscultation, with the condition that personal factors, such as auscultatory experience, fatigue, surrounding noise level, and rhythmic concentration ability, are omitted.

3. The three major forms of cardiac sound modification that are encountered in auscultation may have the following relationships to phonocardiography:

a. In phonocardiography, as in auscultation, the chest factor must be considered as a variable quantity.

b. The modification effects that are introduced by an acoustic stethoscope and its chest pieces in auscultation may be reproduced perfectly by phonocardiography.

c. The logarithmic type of modification that is introduced in auscultation by average normal hearing may also be reproduced by phonocardiography.

4. Phonocardiographic registration may therefore be considered according to the degree of modification introduced, namely:

a. Linear phonocardiography, or the registration of the sound vibrations as they exist on the surface of the chest.

b. Stethoscopic phonocardiography, or the registration of the sound vibrations as they are transmitted to the ears by an average acoustic stethoscope.

c. Logarithmic (human audiographic) phonocardiography, or the registration of sound vibrations as they are perceived by a competent observer if the personal factors are omitted.

5. Linear, stethoscopic, and logarithmic phonocardiography are directly related to auscultation. Each phonocardiographic method is a representation of a definite stage of sound transmission in auscultation. Deviations may be introduced by a phonocardiograph with frequency response characteristics other than linear, stethoscopic, or logarithmic. Such deviations bear no direct relationship to the auscultatory transmission and detection stages. Therefore, a phonocardiograph with other than linear, stethoscopic, or logarithmic characteristics must be considered as either an apparatus of poor design or an expression of the designer's personal opinion, unless the deviation is based upon a natural constant.

6. The linear phonocardiograph is essentially an electrical sphygmograph which possesses several advantageous characteristics not common to the "segment capsule" or "direct optical" type of sphygmograph.

7. A linear phonocardiogram, when registered over the apex, is an "apex cardiogram," or "apex beat" tracing.

8. A chest piece was devised which makes possible simultaneous phonocardiographic registrations over the same precordial area. For example, this dual chest piece is useful for simultaneously registering the apex beat and the stethoscopic or logarithmic phonocardiogram at the apex.

Clinically, such simultaneous registrations may be useful in differentiating between the third heart sound and the opening snap of the mitral valve when the isometric relaxation phase of the left ventricle is shortened by mitral regurgitation. The apex cardiogram is also useful in timing diastolic events, as is venous pulse registration. In some persons it is rather difficult to record the venous pulse; in such cases, the apex cardiogram may be registered instead.

9. The first heart sound is composed of four components, namely:

a. The first, which is caused by residual vibrations of auricular origin.

b. The second, which is produced at the beginning of the isometric contraction phase of the cardiac cycle (closure of the mitral and tricuspid valves).

c. The third, which is caused by the opening of the semilunar valves.

d. The fourth, which is caused by the acceleration of the blood in the arterial vessels during the maximum ejection phase of ventricular systole.

10. The linear phonocardiograph is capable of registering the first and fourth components of the first heart sound efficiently, but is very inefficient in the registration of the second and third components.

11. The stethoscopic phonocardiograph registers the first and fourth components of the first heart sound with some attenuation, but does not obliterate the vibrations. The second and third components are registered distinctly.

12. The logarithmic phonocardiograph obliterates the first and fourth components of the first heart sound of most normal persons, and registers the second and third components distinctly.

13. When a normal person is auscultated, the observer rarely hears the first and fourth components of the first heart sound; the second and third components are well heard. Logarithmic hearing (as indicated by logarithmic phonocardiography) is responsible for this auscultatory condition because of the greater relative attenuation of the low frequency first and fourth components than of the higher frequency second and third components. Logarithmic attenuation of the first and fourth components is of sufficient magnitude to bring them below the level of human audibility.

14. A simultaneous stethoscopic or logarithmic phonocardiogram and venous pulse tracing may serve as a means of differentiating between a prolonged first heart sound and a first heart sound which is followed by a short systolic murmur. In the latter instance, it extends beyond the "e" wave peak.

15. Our observations indicate that the second normal heart sound may be composed of four components, namely:

a. The first vibrations, which represent the beginning of the diastolic fall in pressure with ventricular relaxation.

b. The second group of vibrations, which are caused by the closure of the semilunar valves (termination of ventricular systole).

c. The third group, which are most likely due to the arterial wall and blood column vibrations. An additional, possible source of vibration in this phase of the second heart sound may be the natural period vibration of the chest wall, which may conceivably be set into oscillation by the second component.

d. The fourth component is caused by the opening of the mitral and tricuspid valves.

16. The logarithmic phonocardiogram almost always totally obliterates the first, third, and fourth components of the second heart sound vibrations, whereas the stethoscopic and linear phonocardiograms may show all four components. This indicates that no matter how competent an observer may be, he can hear only the second component of the second heart sound of a normal person because his hearing is logarithmic.

17. Although the duration of the normal second heart sound is nearly equal to that of the first, auscultation makes the second sound appear shorter. This is explained by the fact that, normally, two components are audible in the first heart sound, whereas only one is audible in the second heart sound.

18. A simultaneous phonocardiogram and venous pulse tracing may supply sufficient data for differentiating between a prolonged second heart sound and a second heart sound followed by a short diastolic murmur. In the latter instance, it extends beyond the "v" wave peak, but should not be confused with the vibrations of the normal third heart sound.

19. Stethoscopic and logarithmic phonocardiograms were taken on thirty-three normal university students. Our phonocardiographic measurements were compared with those in the literature. It must be realized that our data are limited to a narrow age group. For a complete study, similar data must be obtained from infancy to old age, and classified accordingly. Also, our phonocardiographic registrations were made only at the apex. A complete analysis should incorporate phonocardiograms at the pulmonic, aortic, and tricuspid areas, as well. However, this study was primarily intended to ascertain the causes of phonocardiographic divergences, and should be considered in this light. This study does indicate the causes of divergent phonocardiographic data in the literature. These are:

a. Nonstandardization of the over-all frequency response of the phonocardiograph.

b. Nonstandardization of the chest pieces.

20. Our observations on the thirty-three normal male students show that:

a. The maximum stethoscopic duration of the first heart sound is 0.165 second. The maximum logarithmic duration is 0.135 second.

b. The minimum stethoscopic duration of the first heart sound is 0.105 second. The minimum logarithmic duration is 0.08 second.

c. In every case, the stethoscopic duration of the first heart sound is longer than the logarithmic.

d. The maximum stethoscopic duration of the second heart sound is 0.145 second. The maximum logarithmic duration is 0.110 second.

e. The minimum stethoscopic duration of the second heart sound is 0.085 second. The minimum logarithmic duration is 0.08 second.

f. In every case, the stethoscopic duration of the second heart sound is longer than the logarithmic.

g. Inasmuch as the stethoscopic duration is longer than the logarithmic for both the first and second heart sounds, duration is a function of phonocardiographic frequency response.

h. The first and second heart sounds are noises composed of a conglomeration of unrelated frequencies. Therefore, it is incorrect to regard such sounds as one would a pure harmonic tone or vibration, which many investigators have attempted to do.

i. The maximum stethoscopic duration of the third heart sound is 0.085 second. The maximum logarithmic duration is 0.05 second.

j. The minimum stethoscopic duration of the third heart sound is 0.03 second. The minimum logarithmic duration is 0.015 second.

k. In every case, the stethoscopic duration of the third heart sound is equal to, or longer than, the logarithmic.

l. The third heart sound registered clearly in 85 per cent of the stethoscopic phonocardiograms, whereas it showed distinctly in 30 per cent of the logarithmic phonocardiograms. This indicates that a competent observer cannot detect a third heart sound as efficiently by auscultation as by stethoscopic phonocardiography.

m. Phonocardiographs of dissimilar over-all frequency response do not register the normal third heart sound with equal efficiency. The greater the low frequency attenuation, the less efficient is the phonocardiograph in the registration of the third heart sound.

n. The larger the diameter of the chest piece, the more efficient is the phonocardiograph as a detector of the third heart sound. A "Bowles" diaphragm type chest piece is extremely inefficient in the detection of the third heart sound. The same conditions hold true in auscultation when the acoustic stethoscope is employed.

o. The maximum stethoscopic interval between the beginning of the second heart sound and the midpoint of the third heart sound is 0.240 second; the logarithmic maximum is 0.185 second. The stethoscopic minimum interval is 0.160 second, and the logarithmic minimum is 0.160 second. The interval difference between stethoscopic and logarithmic methods may be accounted for by the logarithmic attenuation or obliteration effect upon the low frequency first component of the sec-

ond heart sound. Phonocardiographs of dissimilar over-all frequency response, therefore, cannot supply identical measurements of such a nature.

p. In 60 per cent of the stethoscopic phonocardiograms, the first heart sound registered with an amplitude greater than, or equal to, that of the second heart sound. The logarithmic phonocardiograms registered the first heart sound with greater or equal amplitude in 45 per cent of the cases. The logarithmic phonocardiograph, which registers the sounds as they are perceived by a competent observer, ausculting with an acoustic stethoscope at the apex, shows that, in the age group studied, the second heart sound is louder than, or as loud as, the first heart sound in 55 per cent of the cases.

q. In fifty-eight per cent of the stethoscopic phonocardiograms taken at the apex there was a slight trace of systolic murmur. Logarithmic phonocardiography shows a similar systolic murmur in 85 per cent of the cases. These figures indicate that the selective attenuating properties peculiar to human hearing tend to bring out this slight murmur with greater efficiency because of the greater preponderance of higher frequency components in the slight systolic murmur.

r. Eighty-eight per cent of the stethoscopic phonocardiograms registered an auricular sound, whereas the logarithmic phonocardiograms registered this low frequency sound distinctly in 21 per cent of the cases. Auscultation, therefore, is less efficient than stethoscopic phonocardiography as a means of detecting the auricular sound.

21. For maximum accuracy in all types of phonocardiographic analysis, a phonocardiograph capable of registering the heart sounds linearly, stethoscopically, and logarithmically should be employed.

REFERENCES

1. Rappaport, M. B., and Sprague, H. B.: Physiologic and Physical Laws That Govern Auscultation and Their Clinical Application. The Acoustic Stethoscope and the Electrical Amplifying Stethoscope and Stethograph, AM. HEART J. **21**: 257, 1941.
2. Johnston, F. D., and Kline, E. M.: An Acoustical Study of the Stethoscope, Arch. Int. Med. **65**: 328, 1940.
3. Laënnec, R. T. H.: De l'auscultation médiate ou traité du diagnostic des maladies des poumons et du coeur, fondé principalement sur ce nouveau moyen d'exploration, ed. 1, Paris, 1819, Brosson et Chaudé.
4. Hürthle, K.: Über die Erklärung des Cardiogramms mit Hülfe der Herztonmarkirung und über eine Methode zur mechanischen Registrierung der Töne, Deutsche med. Wchnschr. **19**: 77, 1893.
5. Einthoven, W., and Geluk, M. A. J.: Die Registrierung der Herztöne, Arch. f. d. ges. Physiol. **57**: 617, 1894.
6. Frank, O.: Die unmittelbare Registrierung der Herztöne, München. Med. Wchnschr. **51**: 953, 1904.
7. Frank, O.: Der Puls in den Arterien, Ztschr. f. Biol. **46**: 524, 1905.
8. Riseman, J. E. F., and Rappaport, M. B.: Logarithmic Recording of Heart Sounds, Proc. New England Heart Assoc. p. 23, 1939-1940.
9. Einthoven, W.: Die Registrierung der menschlichen Herztöne mittels des Saitengalvanometers, Arch. f. d. ges. Physiol. **117**: 461, 1907.
10. Roos, E.: Über objektive Aufzeichnung der Schallerscheinungen des Herzens, Deutsches Arch. f. klin. Med. **92**: 314, 1908.
11. Weiss, O.: Phonokardiogramme, Slg. anat. physiol. Virtr. Jena, 1909, Gustav Fischer.

12. Gerhartz, H.: Die Registrierung des Herzschalles, graphische Studien, Berlin, 1911, Julius Springer.
13. Kahn, R. H.: Studien am Phonokardiogramme, Arch. f. d. ges. Physiol. **140**: 471, 1911.
14. Lilienstein: Über die akustischen Besonderheiten der Herztöne (Ein neuer Herzkontrollapparat), München. med. Wchnschr. **58**: 1561, 1911.
15. Ohm, R.: Die Verwendung eines Gelatinehäutchens für die Registrierung des Herzschalls, Ztschr. f. exper. Path. u. Therap. **11**: 138, 1912.
16. Eyster, J. A. E.: The Time Relations of the Venous Pulse and the Heart Sounds, J. Exper. Med. **14**: 594, 1911.
17. Kapff, W.: Studien über den Venenpuls, Deutsches Arch. f. klin. Med. **113**: 494, 1914.
18. Bridgman, E. W.: Observations on the Third Heart Sound, Heart **6**: 41, 1915.
19. Strähl, E. O.: Resultate der Registrierung der menschlichen Herztöne nach der Methode W. R. Hess, Deutsches Arch. f. klin. Med. **131**: 230, 1920.
20. Kanner, L.: Untersuchungen über die normalen Herztöne und ihre Beziehungen zum Elektrokardiogramm, Ztschr. f. exper. Path. u. Therap. **22**: 244, 1921.
21. Wiggers, C. J.: Modern Aspects of the Circulation in Health and Disease, ed. 2, Philadelphia and New York, 1923, Lea & Febiger.
22. Schutz, E.: Physiologie der Herztöne (Ergebnisse der Herzschallschreibung), Ergebn. d. Physiol. **35**: 632, 1933.
23. Orías, O.: Registro e interpretación de la actividad cardiaca, Buenos Aires, El Ateneo, ed. 1, 1933, ed. 2, 1936.
24. Segura, A. S.: Registro e interpretación de la actividad cardiovascular en el lactante normal, Cordoba (R. A.) Instituto de Fisiologia, 1937.
25. Wiggers, C. J.: Physiology in Health and Disease, ed. 3, Philadelphia, 1939, Lea & Febiger, p. 538.
26. Wiggers, C. J.: Circulation in Health and Disease, ed. 2, Philadelphia and New York, 1923, Lea & Febiger, p. 247.
27. Frank, O.: Tigerstedt's Handb. der Physiol. Method. II_4: 182, 1913.
28. Weitz, W.: Über die Kardiographie am gesunden Herzen mit dem Frank'schen Apparat, Deutsches Arch. f. klin. Med. **124**: 134, 1917-1918; Über die Kardiographie des pathologischen Herzens mit dem Frank'schen Apparat, Ibid. **124**: 155, 1917-1918.
29. Frank, O., and Hess, O.: Über das Cardiogramm und den ersten Herzton, Verhandl. des Cong. f. Inn. Med. **25**: 285, 1908.
30. Weber, A.: Über das Kardiogramm, Ztschr. f. exper. Path. u. Therap. **21**: 252, 1920.
31. Krönecker: Des méthodes servant à déterminer les manifestations extérieures de l'activité du coeur, Compt. rend. Soc. de biol. **53**: 390, 1901.
32. Crehore, A. C.: A Study of Simultaneous Tracings From the Apex of the Heart and the Radial Artery With the Micrograph, J. Exper. Med. **14**: 339, 1911.
33. Taquini, A. C., Massell, B. F., and Walsh, B. J.: Phonocardiographic Studies of Early Mitral Disease, Am. Heart J. **20**: 295, 1940.
34. Orías, O., and Braun-Menéndez, E.: The Heart Sounds in Normal and Pathological Conditions, London, New York, Toronto, 1939, Oxford University Press.
35. Caeiro, A., and Orías, O.: El fonocardiograma registrado en los distintos focos de auscultación. Sus caracteres y relaciones con el pulso venoso y el electrocardiograma, Rev. argent. de cardiol. **4**: 71, 1937.
36. Billing: On the Auscultation and Treatment of the Affections of the Heart, Lancet **2**: 198, 1831-1832.
37. Rouanet, J.: Analyse des bruits du coeur, Thèse, Paris, **252**: 18, 1832.
38. Webster, C. E.: Note on the Production of the Second Heart Sound, J. Physiol. **3**: 294, 1882.
39. Ohm, R.: Der sog. dritte Herzton und seine Beziehungen zur diastolischen Kammerfüllung, Berl. klin. Wchnschr. **58**: 600, 1921.
40. Frey, W.: Herztöne und Herzgeräusche, Handb. d. norm. u. pathol. Physiol., Julius Springer, Berlin, Abt. VII, T. 1, 267, 1926.
41. Lian, C.: Le troisième bruit du coeur, Semaine d. hôp. de Paris **3**: 596, 1927.
42. Lian, C.: Les rythmes cardiaques physiologiques à trois temps. (Remarques cliniques et phonocardiographiques), Bull. Soc. méd. hôp., Paris **1**: 32, 1934.
43. Gübergritz, M. M.: Vom dritten normalen Herzton, Ztschr. f. klin. Med. **102**: 109, 1925.

44. Melik-Gülnasarian, E. A.: Über den tonus des Herzmuskels und der dritten Herzton. Klinisch-experimentelle Untersuchung, Ztschr. Kreislaufforsch. **24**: 433, 1932.
45. Leonhardt, W.: Über den dritten Herzton und das kindliche Herzschallbild, Ztschr. f. d. ges. exper. Med. **84**: 470, 1932.
46. Schütz, E.: Physiologie der Herztöne (Ergebnisse der Herzschallschreibung), Ergebn. d. Physiol. **35**: 632, 1933.
47. Braun-Menéndez, E., and Orías, O.: Estudio fonocardiográfico en cien adultos jóvenes, Rev. argent. de cardiol. **1**: 101, 1934.
48. Routier, D., and Van Bogaert, A.: Contribution à l'étude clinique du bruit de galop; renseignements fournis par la cardiographie apexienne associée à l'electrocardiographe, Arch. d. mal. du coeur **27**: 389, 1934.
49. Weiss, O., and Joachim, G.: Die Beziehungen der Herztöne und Herzgeräusche zum Elektrokardiogramm, Deutsche med. Wchnschr. **36**: 2187, 1910.
50. Frey, W.: Herztöne und Herzgeräusche, Handb. d. norm. u. pathol. Physiol. Berlin, 1926, Julius Springer, Abt. VII, T. 1, 267.
51. Yoshioka, J.: Graphical Registration of Heart Sounds, Acta scholae med. univ. imp. in Kioto **14**: 252, 1932.
52. Yoshioka, J.: The Analytical Investigation of the Normal Heart Sounds, Acta scholae med. univ. imp. in Kioto **14**: 258, 1932.
53. Braun-Menéndez, E., and Orías, O.: Estudio fonocardiográfico en cien adultos jovenes, Rev. argent. de cardiol. **1**: 101, 1934.
54. Lewis, T.: The Time Relations of Heart Sounds and Murmurs With Special Reference to the Acoustic Signs in Mitral Stenosis, Heart **4**: 241, 1913.
55. Lewis, T.: Illustrations of Heart Sound Records, Quart. J. Med. **6**: 441, 1913.
56. Hess, O.: Untersuchung der Bewegungen des normalen und pathologischen Herzens sowie der zentralen Gefässe mit dem Frank'schen-Apparat, Ergebn. d. inn. Med. u. Kinderh. **14**: 359, 1915.
57. Clerc, A., Zadoc-Kahn, B., and Tavecchi, G.: A propos du troisième bruit du coeur, Compt. rend. Soc. de biol. **116**: 1017, 1934.
58. Duchosal, P.: Nouvelles recherches graphiques sur le bruit de galop, Arch. d. mal. du coeur **28**: 345, 1935.
59. Miller, A., and White, P. D.: Crystal Microphone for Pulse Wave Recording, Am. Heart J. **21**: 504, 1941.
60. Kountz, W. B., Gilson, A. S., and Smith, J. R.: The Use of the Cathode Ray for Recording Heart Sounds and Vibrations. I. Studies of the Normal Heart, Am. Heart J. **20**: 667, 1941.
61. Smith, J. R., Gilson, A. S., and Kountz, W. B.: The Use of the Cathode Ray for Recording Heart Sounds and Vibrations, II. Studies of the Muscular Element of the First Heart Sound, Am. Heart J. **21**: 17, 1941.
62. Smith, J. R., Edwards, J. C., and Kountz, W. B.: The Use of the Cathode Ray for Recording Heart Sounds and Vibrations, III. Total Cardiac Vibrations in One Hundred Normal Subjects, Am. Heart J. **21**: 228, 1941.

OBSERVATIONS ON THE EFFECT OF TOURNIQUETS ON ACUTE CARDIAC CRISES, NORMAL SUBJECTS, AND CHRONIC HEART FAILURE

WILLIAM B. KOUNTZ, M.D., JOHN R. SMITH, M.D., AND SYDNEY T. WRIGHT, M.D.
ST. LOUIS, MO.

DEATH from many forms of cardiac disease may be sudden. This is especially true of such conditions as acute myocardial infarction, paroxysmal left ventricular failure, and pulmonary embolism. It has long been recognized that, if one can tide the patient over the acute stage of the disease by minimizing the demands on the heart, and by the judicious use of supportive measures, his chances of recovery may be considerably enhanced. Acute failure of the left ventricle seems particularly amenable to treatment when it is promptly and vigorously applied. This depends not only on rest and drugs to improve myocardial function, but also, in many instances, on diminishing the work of the heart. It is well established that rapid lowering of venous pressure by phlebotomy[1-6] may produce pronounced relief of symptoms and rapid recovery of myocardial function in acute cardiac dyspnea. Indeed, phlebotomy has been hailed by some as a lifesaving procedure in left ventricular failure, especially when venous engorgement has developed.

It has been stated[6] that the improvement after bleeding is dependent in part on the sudden reduction of venous pressure, which facilitates recovery of the left ventricle and the establishment of a more adequate pulmonary circulation. To be effective, the lowering of venous pressure must be rapid. However, other factors may be involved because the blood volume after venesection may be quickly restored, and yet improvement may be maintained.

The efficacy of phlebotomy in many of these cases suggested to Danzer[7] that a similar effect might be obtained by the application of pneumatic tourniquets to the extremities, thus utilizing the peripheral venous system as a reservoir to decrease the circulating blood volume. His system employed a valve whereby the tourniquets could be inflated to any desired pressure. Danzer reported that this procedure produced a dramatic relief of symptoms in some cases of acute cardiac failure.

From the Department of Internal Medicine, Washington University School of Medicine.

Presented before the seventeenth scientific session of the American Heart Association, Cleveland, May 31, 1941.
Received for publication Oct. 9, 1941.

Weiss and Robb[8] also applied tourniquets to the limbs in cases of acute left ventricular failure. They reported that this measure was more beneficial than phlebotomy from the standpoint of rapid relief of symptoms, although they thought the effects were of shorter duration. We have observed a number of persons with extreme pulmonary edema incident to sudden decompensation of the left side of the heart to whom pneumatic cuffs were applied (by a method described below). The dramatic relief of symptoms left no doubt as to the effectiveness of this procedure in such cases.

Certain advantages of this method over venesection seem to be self-evident. It would appear that more blood could be removed from circulation by utilizing the peripheral venous tree as a reservoir than would be desirable by bleeding alone. Another advantage is that a large quantity of blood may be retained "in storage" for a long period of time. There is the disadvantage that it does tend to cause venous dilatation, and thus might favor the production of venous thrombosis, and possibly emboli.

Acute myocardial infarction is another condition in which reduction of the quantity of blood flow to the heart might be beneficial as an adjunct to enforced rest and sedation in minimizing the demands on the myocardium. *Prima facie* consideration also suggests that the procedure might possibly be useful in cases of extensive pulmonary embolism and cor pulmonale, in which elimination of strain on the right ventricle is sought. Therefore, it seemed that the procedure merited further investigation, and an attempt was made to study the effect of peripheral venous congestion on normal persons and on patients with cardiac disease, with the hope of uncovering some of the physiologic factors which are responsible for the dramatic relief of left ventricular failure when tourniquets are used.

METHOD

The application of tourniquets to the extremities for long periods of time requires that they be released frequently to forestall damage to tissues. For these clinical and experimental observations an instrument* was devised whereby the pneumatic cuffs could be rhythmically inflated and deflated in rotation; this permitted them to be retained in place for many hours without distress to the patient and without entailing the risk of tissue damage. Cuffs 3 inches wide were designed for use on the arms; those for the legs were 6 inches wide; the cuffs were of variable lengths so as to fit any size of limb. The tourniquets were applied as closely proximally as possible to each extremity, and were held in place by canvas straps. A small, double-acting pump maintained air pressure in a reservoir, whence the air was conveyed to the valves and cuffs. The valves were so arranged that the cuffs were kept inflated for four minutes, and were deflated, in rotation, for one minute; therefore, three were always inflated simultaneously. An escape valve on the reservoir could be adjusted to maintain a pressure (in mm. Hg) of any level in the cuffs. It was our custom to utilize the diastolic blood pressure level.

*The instrument used in these experiments was built by the Burdick Corporation.

Studies were made on normal persons and on a group with heart disease. Two of the latter group, with typical signs of mitral stenosis, had hearts of essentially normal size. In the remainder (with hypertensive heart disease and coronary disease) the hearts were definitely enlarged.

Observations on cardiac size and the scope of ventricular motion were carried out by obtaining teleroentgenograms and roentgenkymograms on each patient immediately before the cuffs were applied, and again after they had been in operation for various lengths of time. Care was taken to see that the patient was as nearly as possible in the same position each time a roentgenogram was made, so that changes in heart size and the excursion of the ventricles could be more accurately evaluated.

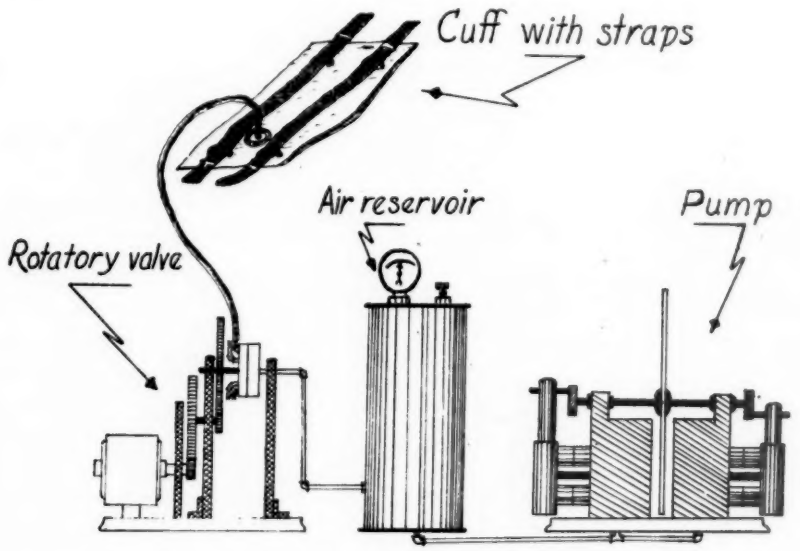


Fig. 1.—Schematic diagram of the instrument.

The arterial blood pressure was carefully measured after the patient had lain quietly and the pulse rate and blood pressure had become stabilized. This was repeated at intervals after application of the tourniquets. Venous pressures were measured with the apparatus described by Lyons, Kennedy, and Burwell.[9] The patient lay supine with the cuffs in place, and the venous pressure was measured in the femoral vein. The latter site for venepuncture was chosen because it enabled the arm cuffs to occupy their usual proximal positions; the cuff on the leg from which the pressure was recorded was placed just below Scarpa's triangle. With the patient lying supine, the level of the femoral veins was approximately the same as that of the right auricle, as shown by measurement.[9] A 3 per cent solution of sodium citrate was utilized in the manometer so that continuous readings could be made without trouble from clotting. The venous pressure was again noted after inflation of the tourniquets.

In a number of patients with normal hearts, both lateral and anteroposterior kymograms were obtained in order to estimate changes in the stroke volume of the heart before and after venous stasis was begun. This will be described in greater detail later.

RESULTS

Effect of Peripheral Venous Stasis on Venous Pressure.—All of the subjects showed a decrease of venous tension after inflation of the tourniquets. The decrease, however, was gradual and had usually

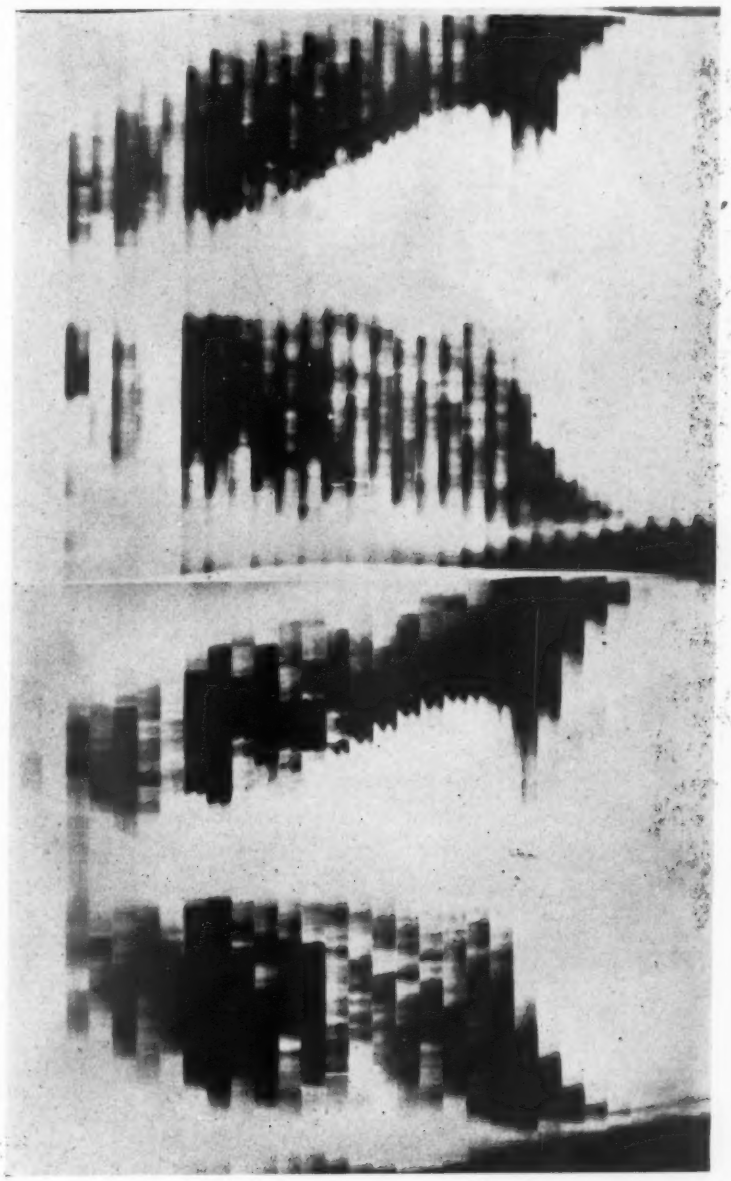


Fig. 2.—*A* is a kymogram of a normal subject before the application of pneumatic tourniquets to the extremities. Note the dense parenchymatous lung markings adjacent to the right ventricle; this should not be construed as part of the heart shadow. *B* is the kymogram of the same person one-half hour after the tourniquets had been in place. Note the increased prominence of the right ventricular border.

reached the maximum point of fall in twenty to twenty-five minutes. This lower pressure was maintained and was not decreased further regardless of how long the procedure was continued. The degree of fall

varied from subject to subject and ranged from 3 to 10 cm. of water. When constriction of the limbs was discontinued, the venous tension gradually rose to its original level in five to eight minutes.

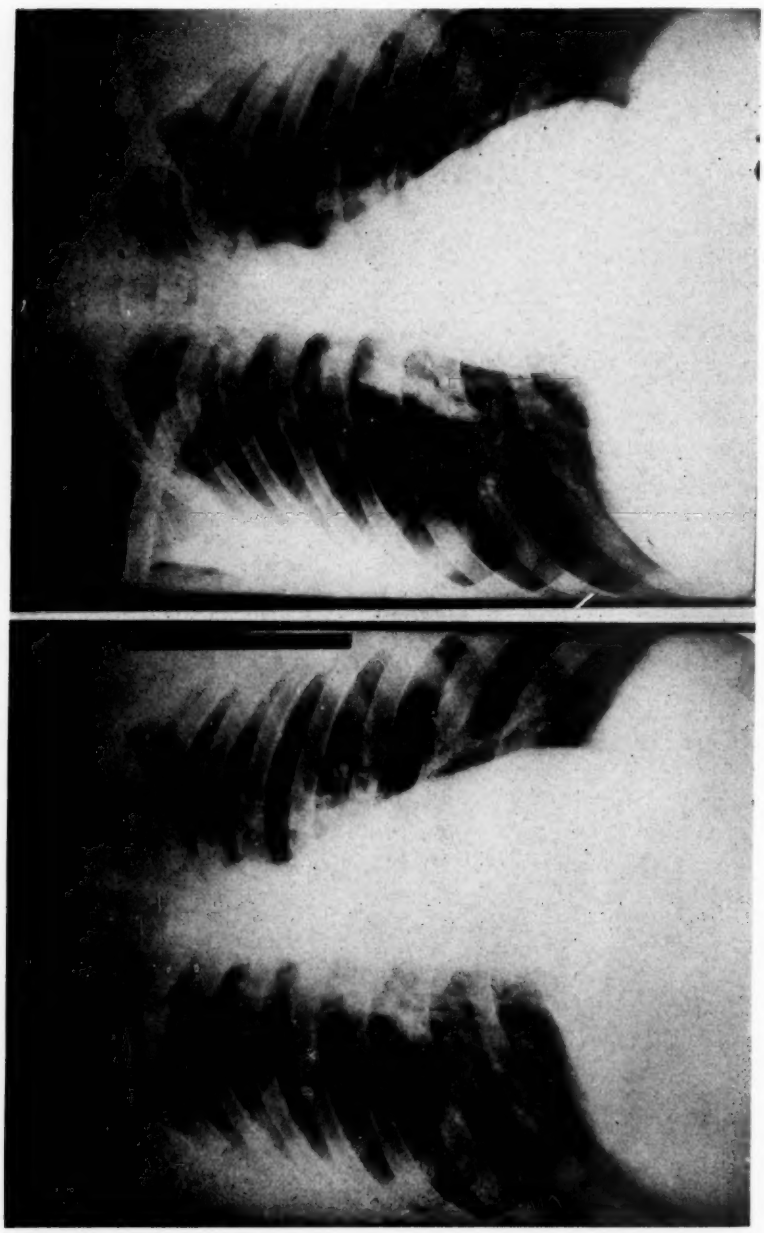


Fig. 3.—Patient with mitral stenosis; heart of normal size. The heart before (*A*) and one-half hour after (*B*) the pneumatic cuffs had been applied. In patients with mitral stenosis the apparent enlargement of the heart was greater during rhythmic venous congestion than in normal persons (see text).

Effect on Arterial Blood Pressure.—Constriction of the extremities of normal persons produced a slight rise of diastolic pressure (10 to 15 mm. Hg), but the systolic pressure was unchanged or somewhat reduced

(0 to 10 mm. Hg). These alterations in pressure were maintained constantly while the tourniquets were in operation; release of the cuffs resulted in prompt restoration of the original pressure level. Patients with blood pressures at hypertensive levels, on the other hand, reacted less uniformly. It seemed generally true that, in hypertension with definite (or marked) cardiac enlargement, the procedure caused a fall of blood pressure (10 to 20 mm. Hg systolic and diastolic); however, in some instances there was essentially no alteration. The pressure changes were maintained while venous congestion was in progress, and prompt restoration to the original blood pressure level occurred on release of the cuffs.

In persons with normal cardiovascular systems and in those with heart disease, *there was no alteration of pulse rate* during the time venous stasis was being maintained.

Effect of Venous Stasis on the Size of the Heart Shadow and on the Contractions Recorded by Kymography.—When the heart was of normal size, intermittent venous congestion resulted in *enlargement* of the cardiac silhouette. From a study of the roentgenograms, this enlargement apparently involved the right ventricle alone, the outline of which became conspicuous to the right of the sternum. There was no demonstrable alteration in the size or shape of the mediastinum or of the pulmonary conus. Of equal interest were changes in the kymograms. The excursions of the cardiac walls were definitely diminished by venous congestion. This appeared to be particularly pronounced in the left ventricle; the decrease in the wavelets of the right ventricle was definite, but less marked. No differences in the essential wave forms were noted in the control roentgenograms and in those taken after the tourniquets were inflated. In all of the cases, the roentgenograms were obtained one-half hour after venous congestion was begun, and those which were made later showed no progression of right ventricular enlargement or change in degree of myocardial motion. Essentially the same phenomenon was noted in the two cases of mitral stenosis, except that the enlargement of the heart after venous stasis was more pronounced. Table I illustrates the increase in size of the normal hearts.

TABLE I

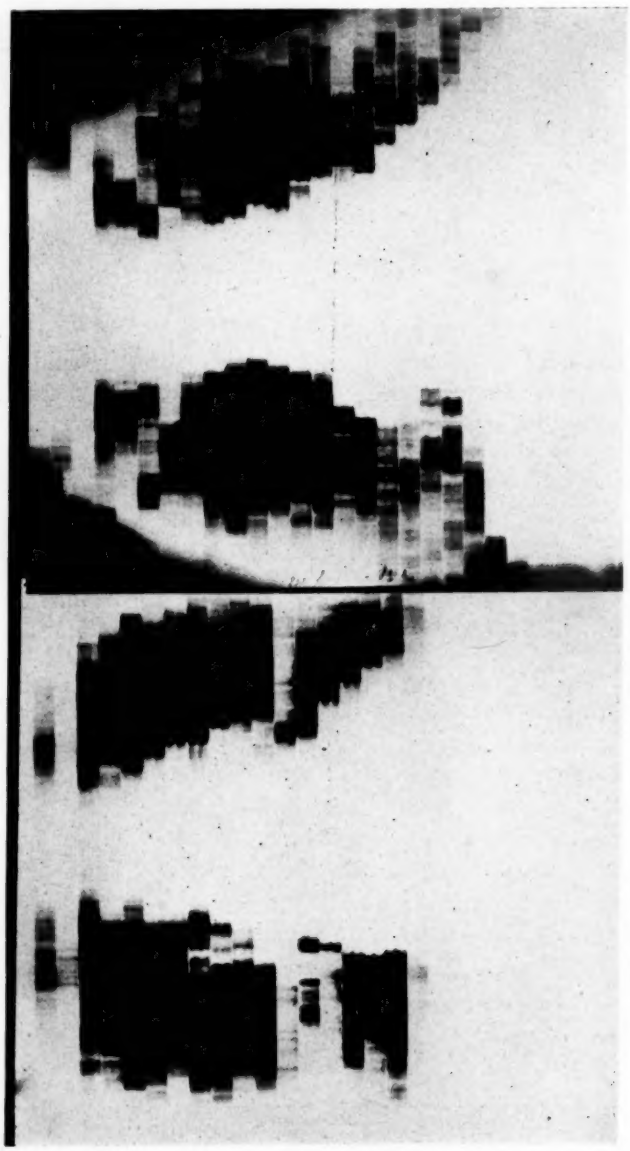
TRANSVERSE DIAMETERS OF HEARTS OF NORMAL SIZE

CASE	BEFORE INTERMITTENT VENOUS STASIS (CM.)	AFTER ½ HOUR OF INTERMITTENT VENOUS STASIS (CM.)
1	12.9	14.6
3	12.3	13.9
6	11.8	13.2
2*	12.6	19.6

*Mitral stenosis (see Fig. 3).

In the cases of hypertension with cardiac enlargement, venous congestion usually produced *no* demonstrable change in the size of the heart;

however, in two instances the cardiac silhouette definitely decreased in size in all dimensions. Kymograms of these enlarged hearts showed a diminution in the amplitude of the movement of the ventricular walls (after establishing peripheral venous stasis with the cuffs), whether the



B.

A.

Fig. 4.—Kymograms of patient with hypertensive heart disease with moderate cardiac enlargement. The heart before (*A*) and after (*B*) inflation of the cuffs for one-half hour. There was no essential change in the size of the heart. Note the diminution in the excursions of the heart wall (*B*).

heart became smaller or not. Nevertheless, the fine patterns of the movements were preserved. In these cases, the diminution of motion appeared to involve the right and left ventricles equally.

The diminution in the excursion of the heart walls made it seem that cardiac output had been reduced. An attempt was therefore made to

estimate the change in cardiac output by means of kymography. Ungerleider and Gubner[11] have recently reviewed the formulas suggested for the estimation of heart volume by measuring certain diameters of the heart in systole and diastole. We utilized the Benedetti formula,

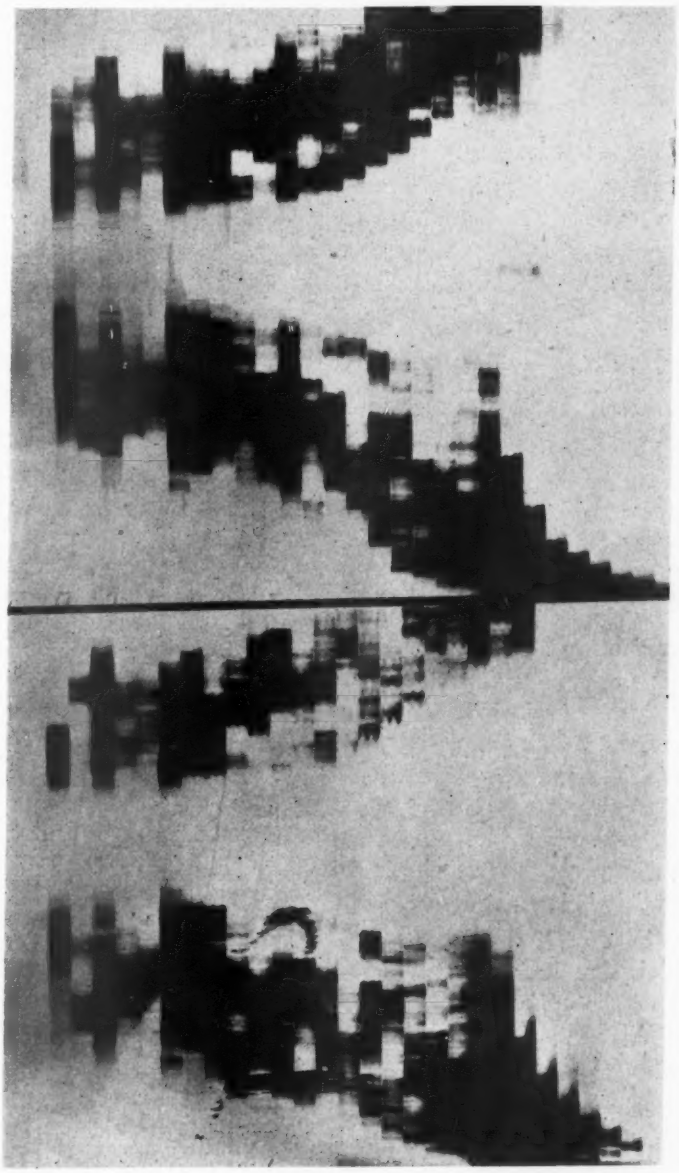


Fig. 5.—Kymograms of a patient with essential hypertension and angina pectoris. After application of the tourniquets (*B*) for one-half hour, the heart was somewhat smaller; the amplitude of the crests and troughs was diminished.

A.

B.

as outlined by them, in studying a group of normal persons to whom the pneumatic cuffs were applied. The details of the procedure need not be repeated here. We are aware that the exactness of our figures may be open to question, because repeated examination of the same per-

son introduced a probable error of position. However, it was found that the estimated output of the heart fell from 25 to 45 per cent after the establishment of venous stasis. That the cardiac output was diminished would seem to be borne out by the fact that a lowering of venous pressure and a diminution in the peaks and troughs in the kymograms occurred without any change in heart rate as blood was held stagnant in the extremities.

Venous Stasis and Improvement in Symptoms.—In some of the cases of marked cardiac enlargement the patients were being treated with digitalis, although their myocardial reserve was so diminished that they suffered from mild dyspnea even at rest, and some had orthopnea. All of them exhibited some signs of pulmonary congestion (a few sibilant and moist râles at the bases of the lungs). During a half-hour period after application of the cuffs, these patients insisted that their shortness of breath disappeared and that they could lie flat without distress. Examination of the chest showed that the signs of congestion were greatly reduced. This improvement was maintained over a period of several hours after the cuffs were removed. In view of the fact that great improvement may be obtained in cases of acute cardiac dyspnea by this method, as noted by Weiss and Robb and by us, it was not surprising that milder pulmonary edema was also benefited.

In a group of cases of acute left ventricular decompensation and pulmonary edema, we noted marked improvement as a result of this procedure. Complicating factors (pneumonia) ultimately caused death in two of eight patients who were studied. In a study of ten patients with acute myocardial infarction, this treatment was given for a period of fourteen days. All of them survived, whereas the mortality rate of such patients, in a hospital from which a similar group of patients was chosen, was 37 per cent. A more detailed study must be made before definite conclusions can be drawn, but these results suggest that this treatment affords some protection to the heart when the function of the *left* ventricle is impaired.

On the other hand, two patients with massive pulmonary embolism were definitely not benefited by the treatment. Both died soon after application of the cuffs. This seemed also to be true of chronic right ventricular disease. Three patients with cor pulmonale caused by pulmonary fibrosis were not improved by intermittent venous stasis.

DISCUSSION

The mechanisms which govern the responses of the cardiovascular system as a whole are so interdependent that it is difficult to separate them. In the evaluation of these experimental data a multitude of factors must be considered, and, in the light of present knowledge, only a suggestion of the meaning of the phenomena can be offered.

A reduction of venous pressure occurred in all of the subjects (proximal to the cuffs) during superficial constriction of the limbs. One would expect this to occur because a large volume of blood may be trapped in the peripheral venous system. Although inflation and deflation of the cuffs in rotation allowed blood to be held in three extremities simultaneously, the quantity of inactive blood was not strictly constant because of the differences in volume of the upper and lower extremities. However, it is possible that as much as an eighth of the total circulating blood volume was impounded.

It seems clear that, in normal subjects, intermittent constriction of the four limbs results in enlargement of the cardiac silhouette. Whether or not the enlargement is limited to the right ventricle, as one might surmise from study of the roentgenograms, is difficult to say. It is possible that both chambers may be increased in size, but that the right is more affected than the left. The work of Eyster and Middleton[12] would lead one to expect that the opposite takes place. These observers noted that the cardiac silhouette decreased in size in donors who were bled an estimated 8 per cent of the total blood volume.

The explanation of cardiac enlargement during intermittent venous congestion of the limbs does not appear to be simple; however, a number of possibilities deserve consideration.

Since our procedure had an obvious physical effect on the vascular system, one might surmise that some change may have occurred which produced overfilling of the ventricles. A second possibility is a disturbance in the nervous relationship which would reflexly stimulate the cardiac nerves and produce cardiac dilatation. The third, and perhaps most likely, explanation is that the physical obstruction leads to the production of chemical factors in the body which are carried by the blood to the heart and cause myocardial dilatation.

The Physical Effect of Cuffs.—The effect of the application of cuffs is to reduce the amount of blood flowing to the heart. This was shown by Ebert and Stead,[10] who demonstrated that as much as one-sixth to one-eighth of the total amount of blood may be impounded in the extremities when they are constricted by tourniquets. Our experiments have verified the fact that as much as one-eighth of the total volume of blood may be held in the periphery. In our studies a decrease in the systemic venous pressure was noted on application of the cuffs. This might indicate that there was a reduced amount of blood flowing to the heart. It would appear logical that the physical effect of the cuffs on the circulating blood volume was not a factor in increasing the size of the heart. The irregularity in the amount of blood returning to the heart (because of the difference in volume of the extremities) would not seem to be a factor in cardiac dilatation because of the small amount of blood that was released at any one time. There was only a slight fluctuation of venous pressure when the individual cuffs were released.

The Influences of Venous Congestion on Cardiac Reflexes.—A reflex mechanism as the cause of the increase in cardiac size appears unlikely. Under the circumstances of our studies it seemed possible at first that the high peripheral pressure in the extremities might have caused cardiac dilatation through reflex vagal stimulation. If such were the case, certainly one would expect other evidence of vagal stimulation, such as slowing of the heart rate. However, the heart rates remained fairly constant when the cuffs were in place.

The Chemical Influence of Blood From Congested Extremities.—A chemical factor as a possible cause of the increase in heart size must be considered. It was interesting that persons who had heart disease (that is, cardiac hypertrophy and dilatation) showed no increase, and frequently a decrease, in cardiac size. Since these patients had heart failure, and many of them showed a slight increase in venous pressure, one might consider that their hearts were already exposed to some factor which was associated with venous congestion. In these cases the application of the cuffs simply produced a mechanical effect by decreasing the amount of blood flowing to the heart and reducing cardiac size and work, and did not increase the size of the cardiac silhouette because of the mild venous congestion which was already present. If such an assumption were true, it would seem to indicate that, in patients with chronic congestive heart failure, there may be a substance in the circulation which causes the heart to dilate.

Normal persons, and those with heart disease without peripheral congestion, responded by an increase in cardiac size. The subjects whose cardiac shadow increased to the greatest extent with application of the cuffs were those whose cardiac size increased maximally during exercise. These subjects had mitral stenosis and always developed increased venous pressure with exercise. These observations were so uniform and persistent that they suggested that the same factor which caused cardiac dilatation with exercise likewise produced it when the cuffs were in place. Since there was just one common condition under both circumstances, that is, peripheral venous congestion, it would seem that this might be the factor. If this were true, a new conception of the cause of cardiac dilatation would be introduced. Increased venous pressure is the primary factor.

It is usually stated that the cause of pathologic cardiac dilatation is an increased load on the myocardium or weakening of the cardiac muscle. Neither of these factors could have been of primary importance in these cases when the cuffs were in place. These studies suggest that peripheral venous congestion produces cardiac dilatation when the blood returns to the heart. The persistence of the changes in each case that we have studied indicates to us that we are dealing with an important cardiovascular mechanism which seems not to have been considered heretofore.

The application of tourniquets to patients with primary right ventricular failure or acute cor pulmonale caused by extensive pulmonary embolus appears to be contraindicated. This would apply to cuffs which are inflated and deflated in rotation, as well as to tourniquets which are tightened all together and held so. An explanation for this is suggested by the work of Fineberg and Wiggers,[13] namely, that, in primary right ventricular failure, a drastic reduction of venous pressure may increase the degree of failure by further diminishing the force of right ventricular contraction, with the result that the right ventricle becomes less able to overcome the resistance of the pulmonary bed.

SUMMARY

1. The application of tourniquets to the extremities of patients with paroxysmal left ventricular failure usually results in dramatic improvement.

2. This procedure was further investigated by means of an instrument which inflated and deflated cuffs, placed on the arms and thighs, in rotation. The effects on venous and arterial pressure, on cardiac size and contraction, and on cardiac output were observed in normal persons and in patients with heart disease. In both groups, rhythmic inflation of the cuffs caused a fall in venous pressure, diminution of cardiac contraction, and a fall in cardiac output; the arterial pressures were essentially unchanged. In normal persons some enlargement of the heart occurred during rhythmic constriction of the extremities; in patients with hypertensive heart disease the size of the heart usually remained unchanged, but, in two instances, the heart diminished slightly in size. A suggestion as to the cause of these phenomena is offered.

3. It is suggested that this procedure may be useful in the treatment of acute myocardial infarction, as well as in paroxysmal cardiac dyspnea. It appears to be of no benefit in right ventricular failure.

REFERENCES

1. Altschule, M. D.: The Pathologic Physiology of Chronic Cardiac Decompensation, Medicine **17:** 75, 1938.
2. Gordon, B.: The Value of Venesection in the Treatment of the Decompensated Heart, Am. J. M. Sc. **170:** 671, 1925.
3. Lemierre, A., and Bernard, E.: Recherches sur les indications et sur l'action physiologique de la saignée, Presse méd. **34:** 704, 1926.
4. Eyster, J. A. E., and Middleton, W. S.: Venous Pressure as a Guide to Venesection in Congestive Heart Failure, Am. J. M. Sc. **174:** 486, 1927.
5. Robertson, H. F., and Fetter, F.: The Effect of Venesection on Arterial, Spinal Fluid, and Venous Pressure With Especial Reference to Failure of the Left and Right Heart, J. Clin. Investigation **14:** 305, 1935.
6. Fishberg, A. M.: Heart Failure, Philadelphia, 1937, Lea & Febiger, p. 708.
7. Danzer, C. S.: The Pathogenesis and Treatment of Dyspnea in the Light of Recent Experiments, Ann. Int. Med. **2:** 239, 1928.
8. Weiss, S., and Robb, G. P.: Treatment of Cardiac Asthma (Paroxysmal Cardiac Dyspnea), M. Clin. North America **16:** 961, 1933.
9. Lyons, R. H., Kennedy, J. A., and Burwell, C. S.: The Measurement of Venous Pressure by the Direct Method, Am. Heart J. **16:** 675, 1938.
10. Ebert, R. V., and Stead, E. A.: The Effect of the Application of Tourniquets on the Hemodynamics of the Circulation, J. Clin. Investigation **19:** 561, 1940.

11. Ungerleider, H. E., and Gubner, R.: Teleoroentgen Kymograph. Its Application to the Study of Heart Size, Output, and Aortic Elasticity, Radiology **33**: 497, 1939.
12. Eyster, J. A. E., and Middleton, W. S.: Cardio-Vascular Reactions to Hemorrhage and Transfusion, Am. J. Physiol. **68**: 581, 1924.
13. Fineberg, M. H., and Wiggers, C. J.: Compensation and Failure of the Right Ventricle, AM. HEART J. **11**: 255, 1936.

DISCUSSION

DR. WILLIAM S. COLLENS, Brooklyn, N. Y.—I should like to congratulate the authors, and wish to say that Dr. Shapiro, in our clinic, recently conducted the same kind of studies and came to the same conclusions. He used the apparatus which we devised for intermittent venous occlusion, and modified it by attaching four cuffs to it. Three cuffs were inflated at one time while one cuff was deflated in sequence.

DR. WILLIAM B. KOUNTZ.—The method was devised primarily as a technique in reducing cardiac activity, or work. We were very much interested to note that, in left ventricular failure, one not infrequently found that the patient was greatly improved. We extended this to a group of patients who had coronary thrombosis. We had a rather nice control series, because the group was chiefly at the city infirmary, where about 26 per cent of all patients with coronary thrombosis died soon after the shock of coronary occlusion. By using this technique, we found that we could reduce that mortality considerably.

THE INFLUENCE OF XANTHINE DRUGS AND ATROPINE ON THE MORTALITY RATE AFTER EXPERIMENTAL OCCLUSION OF A CORONARY ARTERY

GEORGE V. LEROY,* M.D., G. K. FENN, M.D., AND N. C. GILBERT, M.D.
CHICAGO, ILL.

THERE is still considerable difference of opinion among clinicians concerning the value of the xanthine drugs, theobromine and theophylline, in the treatment of diseases of the coronary arteries and angina pectoris. With respect to the latter, reports have been published recently by Gilbert and Kerr,[1] Brown and Riseman,[2] Massel,[3] Levy and his associates,[4] and LeRoy[5] which strongly advocate the use of these drugs. On the other hand, Master, Jaffe, and Dack[6] and Gold and his associates[7] believe that these same drugs are of little or no value in the management of angina pectoris. In the standard textbooks of medicine one finds the same divergence of opinion. Less has been published recently about the use of these agents in the early treatment of acute myocardial infarction caused by occlusion of a coronary artery. Just as in the discussions of angina pectoris, the textbooks express discordant views about the use of these drugs after myocardial infarction. In fact, some of the books, and some clinicians, foster the impression that, since the blood flow is completely interrupted by coronary occlusion, there is no rationale for the use of vasodilating agents. The experimental literature is scanty and is not of one accord. Gold and his associates[8] have published evidence which demonstrates that the xanthines are of no value. Fowler, Hurevitz, and Smith,[9a] however, reported striking benefits in their series of experiments. It is obvious that, if the rationale for the use of the xanthines in angina pectoris is the ability of these drugs to augment the coronary blood flow, they should be of equal or greater value in the treatment of acute myocardial infarction. Recent anatomic studies[10] of coronary occlusion and myocardial infarction have disclosed the fact that, in 40 per cent of the cases of infarction, the closure of the coronary artery was not complete. Such patients certainly should be helped by drugs that decrease the peripheral resistance in the coronary circulation. Studies by Hall and his associates[11] suggest another very important theoretical reason for the administration of drugs which are capable of augmenting the coronary blood flow in cases of recent infarction of the myocardium. They showed that the mortality rate after experimental occlusion of a coronary artery in dogs may be strikingly modified by

From the Laboratory of Experimental Medicine, the Department of Medicine, Northwestern Medical School, Chicago.
Received for publication Oct. 9, 1941.
*Searle Research Fellow.

cardiosensory denervation. In their conscious animals there was a 75 per cent mortality after ligation of the circumflex branch of the left coronary artery. Bilateral stellate ganglionectomy and upper thoracic sympathectomy reduced this rate to 25 per cent. It was their opinion that a myocardial infarct acted as a stimulus to a reflex whose afferent portion was the cardiosensory nerves, whose efferent portion was the vagus nerves, and whose effect was a reflex constriction of the coronary arteries supplying the uninfarcted myocardium. In all of their experiments, death, when it was observed, was due to ventricular fibrillation, which was induced in part, or entirely, they believe, by generalized myocardial ischemia caused by the reflex coronary vasoconstriction. This hypothesis has been corroborated in three ways by work done in our laboratory: (1) In colored motion pictures of a dog's heart, taken during and immediately after coronary ligation, a definite darkening of the color of the uninfarcted myocardium can be clearly seen just before the onset of ventricular fibrillation.[12] (2) In a report to be published soon, one of us (G. V. L.) has demonstrated that, in conscious dogs, there is a periodic decrease in the blood flow through the circumflex branch of the left coronary artery shortly after occlusion of the anterior descending branch. (3) Finally, in the present report, we shall show that drugs which are known to cause coronary vasodilatation in the dog have practically the same influence on the mortality rate after coronary occlusion as does cardiosensory denervation.

Our position in regard to the use of the xanthine drugs in the treatment of myocardial infarction may be stated briefly as follows:

1. After occlusion of one coronary artery, reflex vagal vasoconstriction of the arteries in the uninfarcted myocardium occurs, and the resulting ischemia is responsible for the early, sudden death of victims of myocardial infarction.

2. Certain drugs decrease the mortality rate in dogs after experimental coronary occlusion.

3. These drugs are known to be capable of increasing the coronary blood flow.

4. Therefore, they influence the mortality rate by augmenting the coronary flow and preventing the general ischemia of the myocardium which may occur reflexly after coronary occlusion.

5. Since these drugs do this, they are useful in the treatment of acute myocardial infarction and angina pectoris.

Throughout this paper, the phrase "mortality rate" has a special meaning. To make our data comparable to those of Hall, et al.,[11] we classify as sudden or reflex deaths those that occur within twenty-four hours after coronary occlusion. Only these deaths are counted in the calculation of the mortality rate. When this is done, the mortality rate after performing coronary occlusion upon anesthetized animals varies from 25 per cent to 100 per cent. Since the chief factor in the causation

of this type of sudden death is reflex vagal vasoconstriction, the depth and the nature of the anesthesia are important. McEachern, Manning, and Hall[11] reported a mortality rate of 75 per cent after producing coronary occlusion in conscious dogs. In our laboratory the rate after a similar procedure was 70 per cent. Because the suffering of a conscious dog with a myocardial infarct is often distressing and disturbing, we sought an anesthetic technique which, by preserving autonomic reflex activity, would yield the same mortality rate. The morphine-nembutal anesthesia that we now use does this.

The experimental procedure is as follows: One-half hour before operation, morphine sulfate in the amount of 1.0 mg. per kilogram is given subcutaneously to healthy dogs. Fifteen minutes later a solution of nembutal (60 mg. per cubic centimeter) is injected slowly intravenously until the corneal reflex just disappears. A tracheal catheter is then inserted for providing positive pressure ventilation with oxygen when the thorax is opened. With aseptic precautions the thorax and the pericardial sac are opened from the left side. With as little trauma as possible a linen ligature is placed around the circumflex branch of the left coronary artery 1.0 to 2.0 cm. distal to its origin. If occlusion is to be produced in the conscious animal on a subsequent day, one hitch is taken in the ligature and the loose ends are passed out through the wound. If the occlusion is to be produced under anesthesia, the ligature is tied tightly at once. The pericardium and the thorax are then closed, and the animal is allowed to recover from the anesthesia if it survives.

The drugs the effects of which were studied were administered in several ways:

1. To some anesthetized dogs the xanthines were given intramuscularly before and/or after occlusion of the artery. For details, see Table II.

2. To some anesthetized dogs the xanthines were given orally for three to fifteen days before operation. Some of these animals also received the drugs intramuscularly immediately after occlusion.

3. To some anesthetized animals, atropine sulfate was given in doses of 0.2 mg. per kilogram intramuscularly immediately after occlusion of the artery.

4. To some conscious dogs a xanthine-atropine mixture was given intravenously five minutes after the occlusion. In other experiments, only atropine was given.

The results of these experiments are collected in Tables I and II.

It is apparent from an inspection of the data that the three drugs which are capable of influencing coronary blood flow, namely, theobromine sodium acetate, theophylline ethylenediamine, and atropine sulfate, modified the mortality rate after experimental coronary occlusion. The most pronounced effect was observed when theobromine sodium acetate was used. If the animal was "saturated" with the drug as a result of oral administration for several days before the occlusion, and intramuscular injection immediately thereafter, there was no mortality (five dogs). When none of this drug was given after the occlusion, two of four died. When the drug was given only immediately before and after the artery was ligated, three of twelve dogs died. The aggregate mortality rate for all dogs which received theobromine sodium acetate was 23 per cent.

The effectiveness of theophylline ethylenediamine was less when it was given in a similar manner. The aggregate mortality for all the

animals that received this drug was 56 per cent. There is a curious similarity between these figures and the data published by LeRoy and Speer.[13] Using a method which measured the coronary sinus outflow, they found that 60 mg. of theobromine sodium acetate, given intravenously, augmented the coronary outflow by an average amount of 150 per cent. Similar quantities of theophylline ethylenediamine increased the flow by 60 per cent. Thus it is apparent that, for the dog, as shown by two types of experiments, theobromine sodium acetate is about twice as effective as theophylline ethylenediamine.

TABLE I

COLLECTED DATA

TYPE OF EXPERIMENT	NO. OF DOGS	SUDDEN DEATH IN 24 HOURS	MORTALITY RATE (%)
A. Anesthetized Dogs			
Controls	13	9	70
Xanthine treated	39	15	38
Theobromine treated	21	5	23
Theophylline treated	18	10	56
Atropine treated	8	3	34
B. Conscious Dogs			
Control	13	9	70
Atropine treated	4	2	50
Treated with theophylline-atropine mixture	6	2	33

TABLE II

DETAILS OF THE ADMINISTRATION OF THE XANTHINES

TYPE OF EXPERIMENT	DOSE	NO. OF DOGS	SUDDEN DEATHS IN 24 HOURS
A. Theobromine Sodium Acetate Group			
After occlusion	120 mg. I.M.	4	1
Before and after occlusion	120 mg. I.M. each time	8	2
Several days before	450 mg. orally daily	4	2
Several days before and after	450 mg. orally 120 mg. I.M.	5	0
Totals		21	5 (23%)
B. Theophylline Ethylenediamine Group			
After occlusion	120-360 mg. I.M.	3	2
Before and after occlusion	120-240 mg. I.M. each	2	1
Several days before	200-300 mg. orally, daily	2	1
Several days before and after	200-300 mg. orally 120-240 mg. I.M.	11	6
Totals		18	10 (56%)
All xanthine treated dogs		39	15 (38%)

I.M., Intramuscularly.

We thought it very desirable to study the effect of atropine sulfate on the mortality rate after experimental coronary occlusion. This drug, through its ability to paralyze vagus nerve branches that transmit tonic or reflex vasoconstrictor impulses to the coronary arteries, is a definite

coronary vasodilator.[14] The increase in coronary flow after the administration of atropine is less than 50 per cent, but the duration of its action is much longer than that of a single intravenous dose of one of the xanthines. In anesthetized dogs, it was found that, when atropine was given intramuscularly five minutes after occlusion, the mortality rate was 34 per cent. It is probable that this effect would have been more striking had the drug been given earlier. In conscious dogs which were given atropine sulfate (0.1 mg. per kilogram) five minutes after occlusion the mortality rate was 50 per cent. There is no apparent explanation for this difference, but it was noted that dogs which were receiving atropine alone appeared to experience much more pain than when atropine and a xanthine were given. Another group of conscious dogs were given a mixture of 120 mg. of theophylline ethylenediamine and 0.1 mg. per kilogram of atropine sulfate intravenously five minutes after arterial occlusion. This was done to simulate clinical practice, where the xanthine available for intravenous use is theophylline ethylenediamine. The effectiveness of this mixture was apparent, for the mortality rate in dogs so treated was 33 per cent, whereas, in untreated ones, the rate was 70 per cent.

We have shown, therefore, that either of two means of preserving an adequate blood flow to the uninfarcted myocardium will reduce the mortality rate after a standard type of myocardial infarction caused by occlusion of a coronary artery. The mortality rate after these procedures closely parallels that reported by McEachern, Manning, and Hall[11] after bilateral cardiosensory denervation. In their conscious dogs, denervation reduced the mortality rate from 75 per cent to 25 per cent after a similar type of coronary artery occlusion. They assumed that this improvement was brought about by preventing reflex vagal vasoconstriction in the uninfarcted myocardium. They believe, as we do, that ischemia of the uninfarcted myocardium initiates the ventricular fibrillation which causes the sudden death of animals with myocardial infarcts. We have shown that atropine exerts a similar protective effect, presumably by inhibiting the effector (vagal) portion of the reflex. Similarly, the xanthines, which have no influence on any of the nervous elements of the reflex, but actively dilate coronary arteries by direct action, have also a protective effect. The more potent vasodilator (theobromine sodium acetate) has a more pronounced effect than the less potent one. Furthermore, in conscious animals the combination of atropine and theophylline reduced the mortality rate to a greater extent (33 per cent) than did either component of the mixture alone (atropine, 50 per cent; theophylline, 56 per cent). This last observation was particularly gratifying because it is our current practice to use a comparable mixture for the treatment of patients with acute myocardial infarction. These experiments seem to us to demonstrate clearly that the production of vasodilatation, or the inhibition of vasoconstriction, in the

uninfarcted portions of the myocardium after coronary occlusion tends to prevent the development of fatal ventricular fibrillation. They also demonstrate that this beneficial effect may be achieved by drugs of the xanthine series alone, or by atropine sulfate alone, or by a combination of the two. There appears to be little difference between the efficacy of the two types of drugs, whose only common feature is their ability to augment the coronary blood flow. Finally, it should be evident from this work that the sooner coronary vasodilatation is achieved, or vasoconstriction prevented, the more beneficial will it be. This is especially true because the primary idea in this type of therapy is to overcome or prevent the reflex vasoconstriction in the uninfarcted myocardium. It is the reflex vasoconstriction that causes the myocardial ischemia and the ventricular fibrillation which is the chief cause of early, "sudden" death in cases of coronary occlusion.

SUMMARY AND CONCLUSIONS

1. The mortality rate in dogs after occlusion of the circumflex branch of the left coronary artery is about 70 per cent. This rate was the same in our experiments for conscious dogs and dogs which were lightly anesthetized with morphine and nembutal.

2. The administration of theobromine sodium acetate to a dog before and/or after experimental coronary occlusion reduces the mortality rate to 23 per cent.

3. The administration of the less potent theophylline ethylenediamine, under similar circumstances, reduces the mortality rate to 56 per cent.

4. The administration of atropine sulfate reduces the mortality rate in anesthetized dogs to 34 per cent, and, in conscious dogs, to 50 per cent, after coronary occlusion.

5. The administration of a mixture of theophylline ethylenediamine and atropine sulfate to conscious dogs five minutes after arterial occlusion reduces the mortality rate from 70 per cent to 33 per cent.

6. The mortality rate after experimental occlusion of the circumflex branch of the left coronary artery in dogs may be considerably reduced by drugs which are capable of causing coronary vasodilatation, or preventing coronary vasoconstriction. Such drugs are the xanthines and atropine sulfate.

REFERENCES

1. Gilbert, N. C., and Kerr, J. A.: Clinical Results in the Treatment of Angina Pectoris With the Purine Base Derivatives, J. A. M. A. **92**: 201, 1929.
2. Brown, M. G., and Riseman, J. E. F.: The Value of Purine Derivatives in the Treatment of Angina Pectoris, J. A. M. A. **109**: 256, 1937.
3. Massel, H. M.: Clinical Observations on the Value of Various Xanthines in Angina Pectoris, J. Lab. & Clin. Med. **24**: 380, 1939.
4. Levy, R. L., Bruenn, H. G., and Williams, N. E.: The Modifying Action of Certain Drugs on the Effects of Induced Anoxemia in Patients With Coronary Insufficiency, AM. HEART J. **19**: 639, 1940.
5. LeRoy, G. V.: The Effectiveness of the Xanthine Drugs in the Treatment of Angina Pectoris. I. Aminophylline, J. A. M. A. **116**: 921, 1941.

6. Master, A. M., Jaffe, H. L., and Dack, S.: The Drug Treatment of Angina Pectoris Due to Coronary Artery Disease, Am. J. M. Sc. **197**: 774, 1939.
7. (a) Gold, H., Kwit, N. T., and Otto, H.: The Xanthines in the Treatment of Cardiac Pain, J. A. M. A. **108**: 2173, 1937.
(b) Gold, Harry: Drug Therapy in Coronary Disease, J. A. M. A. **112**: 1, 1939.
8. Gold, Harry, Travell, J., and Modell, W.: The Effect of Theophylline With Ethylenediamine on the Course of Cardiac Infarction Following Experimental Coronary Occlusion, AM. HEART J. **14**: 284, 1937.
9. (a) Fowler, W. M., Hurevitz, H. M., and Smith, F. M.: Effect of Theophylline Ethylenediamine on Experimentally Induced Cardiac Infarction in the Dog, Arch. Int. Med. **56**: 1242, 1935.
(b) Smith, F. M., Rathe, H. W., and Paul, W. D.: Theophylline in the Treatment of Diseases of the Coronary Arteries, Arch. Int. Med. **56**: 1250, 1935.
10. Master, A. M., Gubner, R., Dack, S., and Jaffe, H. L.: Differentiation of Acute Coronary Insufficiency With Myocardial Infarction From Coronary Occlusion, Arch. Int. Med. **67**: 647, 1941.
11. (a) Manning, G. W., McEachern, C. G., and Hall, G. E.: Reflex Coronary Artery Spasm Following Sudden Occlusion of Other Coronary Branches, Arch. Int. Med. **64**: 661, 1939.
(b) McEachern, C. G., Manning, G. W., and Hall G. E.: Effects of Sudden Occlusion of Coronary Arteries Following Removal of the Cardiosensory Pathways, Arch. Int. Med. **65**: 661, 1940.
12. To illustrate "Sudden Death of Patients With Few Symptoms of Heart Disease" by G. V. LeRoy and S. S. Snider; read before Section for Practice of Medicine, A. M. A. Cleveland, 1941.
13. LeRoy, G. V., and Speer, J. H.: A Comparison of the Coronary Vasodilator Activity of Certain Alkyl Xanthines, J. Pharmacol. & Exper. Therap. **69**: 45, 1940.
14. Essex, H. E., Wegria, R. G. E., Herrick, J. F., and Mann, F. C.: The Effect of Certain Drugs on the Coronary Blood Flow of Trained Dogs, AM. HEART J. **19**: 554, 1940.

A CRITIQUE OF THE PLETHYSMOGRAPHIC METHOD OF MEASURING BLOOD FLOW IN THE EXTREMITIES OF MAN

M. LANDOWNE,* M.D., AND L. N. KATZ, M.D.
CHICAGO, ILL.

TWO types of methods are available for the quantitative measurement of blood flow in the extremities of man. The first depends upon the measurement of the thermal exchange of the extremity, and the second, on the change in the volume of the limb after obstruction of the venous outflow.

The Calorimetric Method.—The enclosed calorimetric method[1] presents certain disadvantages: (a) The assumption that the venous blood is at skin temperature after equilibration is not valid[2, 3]; (b) the insulation is not complete and a variable gain or loss of heat may occur[4]; (c) conduction and radiation cannot be evaluated[5]; and (d) a rapid succession of events cannot be studied.[5]

Surface calorimetry, when utilized under carefully controlled conditions, and when other thermal factors are considered,[5-13] is an important indirect method. The interpretation of thermometric studies of *deep* structures in terms of blood flow[14] is difficult because the origin and dissipation of the heat of these regions may depend partly on other factors. Local metabolism[15] and conduction[5] may play a significant role. Large changes in blood flow may be represented by small changes in deep temperature, for tissue temperatures are close to blood temperature.

The plethysmographic principle, although it has its limitations and disadvantages, seems more suitable as a convenient method of measuring limb blood flow.

The Plethysmographic Method.—Not until recently have criteria been presented for more precise studies of plethysmography, and some of the errors have been corrected.[16-18] An excellent analysis has been made by Wright and Phelps.[18] Realizing the need for a critical evaluation of plethysmography, we have independently endeavored to make a fundamental analysis of the method in order (a) to afford a critique for all general blood flow studies, especially those employing the principles of plethysmography, and (b) to ascertain the limits of technical accuracy which can be attained by a properly constructed and properly employed plethysmograph.

From the Cardiovascular Department, Michael Reese Hospital, Chicago.
Aided by the A. D. Nast Fund for Cardiac Research.
Received for publication Oct. 14, 1941.
*Emanuel Libman Fellow.

The method which we employed is that of Brodie and Russell,[19] as used by Hewlett and van Zwaluwenburg,[20] for application to the extremities, with its subsequent modifications. In principle, the method determines the amount of blood flowing into an extremity by measuring the rate of volume increase of the limb in the plethysmograph when blood is prevented from leaving the part.

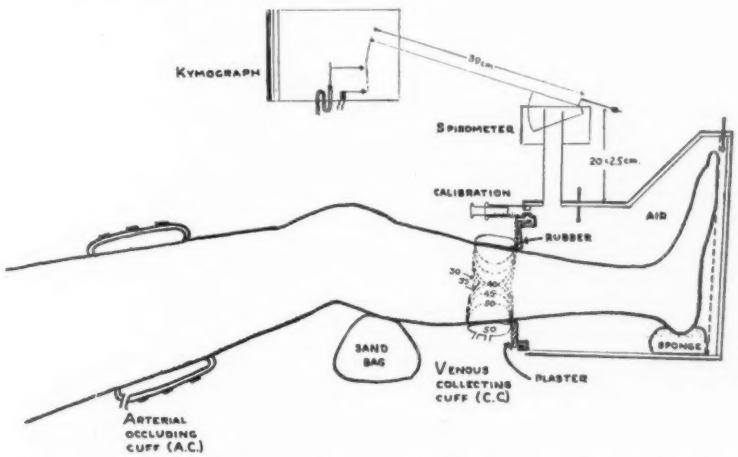


Fig. 1.—Diagram of plethysmograph used to measure blood flow in foot-leg (not to scale). It also indicates the order of magnitude of distribution of pressure in the limb, in mm. Hg, beneath the occluding cuff when the pressure in the latter is 50 mm. Hg. Discussed in text.

In practice, the limb is placed in a plethysmograph which is arranged to record changes in volume (Fig. 1). A pneumatic cuff [collecting cuff (C.C.)] is placed around the limb proximal to the plethysmograph; when this is abruptly inflated to a pressure sufficient to occlude venous outflow but not to impede arterial inflow, an increase in limb volume occurs. The rate of this volume increase indicates the rate of blood inflow. After a few seconds the rate of this volume increase declines. This results from the limited distensibility of the vascular and other tissue structures, and comes about in two ways: (a) Capillary and venous pressures rise and finally exceed the pressure imposed by the collecting cuff, with a resultant escape of blood through the veins; (b) a slowing of blood inflow occurs because of the increasing resistance in the distended limb.* Secondary changes in the extremity may further modify the volume changes. Such changes may include alterations in vascular tone, alterations in fluid balance between the vessels and extravascular

*The recent studies of Linton, et al.,[21] who used the thermostromuhr to measure arterial inflow in the intact dog hindlimb, indicate that an immediate *increase* in arterial inflow follows venous obstruction. These observations would invalidate the fundamental premise upon which the plethysmographic method is based. It is difficult for us to accept this evidence, however, for it purports to demonstrate that a local increase in flow follows the production of a decrease in pressure gradient over the segment studied, in the absence of changes elsewhere. It is also difficult to comprehend how, with the femoral, external iliac, and common iliac veins ligated, blood could continue to enter the iliac artery at a rate of 210 to 215 c.c. per minute over the last minute and a half of maintained occlusion with apparently no place to go.

spaces which may develop during the period of occlusion, and secondary changes in systemic blood pressure and flow.

The essential assumption which is made is that the rate of volume increase during the first few seconds *after* venous occlusion is equal to the unimpeded rate of blood flow obtaining *just prior* to the venous occlusion. In order that this assumption be valid, the collecting cuff must prevent all venous outflow long enough to permit measurement of blood flow without at the same time significantly impeding the inflow of blood.

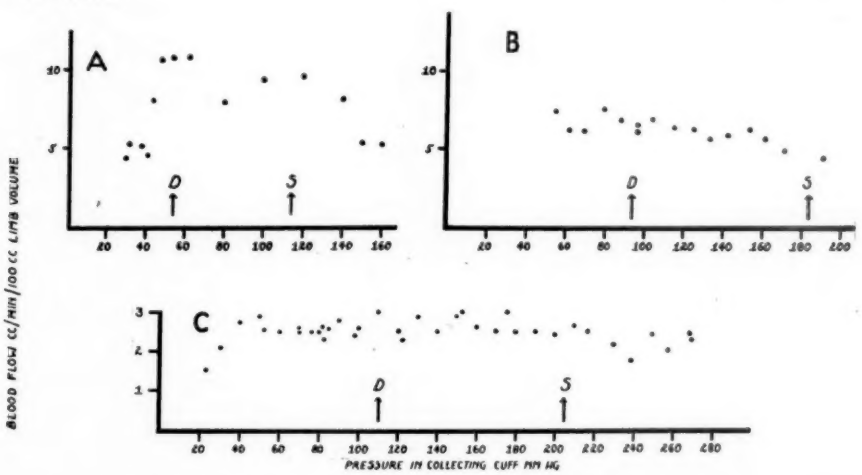


Fig. 2.—Effect of varying the pressure in the collecting cuff (see Fig. 1) on the recorded blood flow in normal subjects (*A* and *B*) and in a subject with hypertension and Raynaud's syndrome, after sympathectomy (*C*). *D* and *S*, in each instance, indicate diastolic and systolic blood pressure levels. Discussed in text.

1. In order to *prevent venous outflow,* several factors must be considered:

(a) *The inflation of the collecting cuff must be prompt.*—This is practiced universally.

(b) *The pressure in the collecting cuff must occlude all of the veins.*—It has been assumed that a pressure in the collecting cuff somewhat below diastolic pressure is effective. This was based upon the observation that the apparent blood flow increases with increasing cuff pressures to a "constant" value at cuff pressures of 50 to 100 mm. Hg.[17, 20] Our studies with a wider range of cuff pressures generally corroborate this; a maximal plateau extending from 50 to 120 mm. or more is observed (Fig. 2*A* and *B*). As expected, in hypertension this plateau was found to extend to a higher level. The results, however, are sufficiently variable to permit the alternative explanation that the degree of venous occlusion is incomplete, and, although it is increased by the higher cuff pressures, its effect is neutralized by a parallel decrease in arterial inflow. Although the externally applied pressure which is necessary to obstruct a brachial artery is only slightly above the

pressure within this vessel,[22] and veins are more collapsible than arteries, no direct evidence has been presented that complete venous occlusion is actually accomplished by the collecting cuff inflation. This factor is to be considered, especially when two long bones partially shield large vessels, as is the case in the forearm and calf. Lewis[23] found, however, that the venous pressure rise after cuff inflation was prompt, and, as was also noted by Levy and Brams,[24] reached the pressure level in the cuff, indicating that the deeper veins were distended. Evidence of a different sort, pointing to the same conclusion, has been obtained by us. A 9 cm. cuff was placed about the calves of several living subjects and one cadaver, and tissue pressures were measured within the calf beneath the cuff. A long needle was inserted for this purpose at the cuff margin or through an eyelet in the center of the cuff, and the pressures were measured directly at various directions and distances.[25] The distribution of pressure under such an inflated collecting cuff is outlined in Fig. 1; there is a slight pressure gradient toward the center beneath the cuff, and a steeper one toward the sides. This evidence suggests that, at 50 mm. Hg of cuff pressure, the pressure distribution in the tissue beneath the cuff would be sufficient to occlude all collapsible veins. No evidence is adduced from this study as to the effect upon blood pathways in bone, or as to the minimum effective width of the cuff. A test of the adequacy of cuff width was undertaken by comparing the apparent blood flow in a normal subject with a 9 cm. and a 5 cm. cuff of the type described by Abramson, et al.[17] The flow with the wide cuff was 3.2 to 4.1, and, with the narrow cuff, 3.9 to 4.2 c.c./min./100 c.c. of limb volume.

(c) *The pressure in the collecting cuff must not decrease arterial inflow.*—Our experiments on the effect of increasing cuff pressure on apparent blood flow in normal subjects (Fig. 2) and in patients with hypertensive vascular disease showed that the blood flow measurement was sometimes the same until cuff pressures well above the systolic blood pressure were reached. Above this point the blood flow measurements decreased, indicating obstruction of arterial inflow. It would therefore appear that arterial inflow at the moment of inflation of the cuff is not altered with the cuff pressures ordinarily employed.

2. Even if the venous occlusion is complete, there must be a *sufficient period of time to make a blood flow measurement* before the rate of blood accumulation is significantly altered. From purely physical considerations, as soon as an impediment is placed in the path of flowing fluid, a readjustment of the pressure in the entire fluid system occurs. The validity of the assumption that this does not significantly alter the rate of blood flow during the first few seconds after the application of venous occlusion would require that the change in distribution of pressure be small. No such evidence has been presented. In practice, the interval immediately after cuff inflation is usually not utilized because

of the presence of artifacts at this time. It is the custom to use the average rate of volume increase during the three or four seconds after the initial artifact.

The volume curve of the leg after venous occlusion appears as a curve in relation to time. If the equation for this curve were known, its first differential would indicate the rate of change in volume with time, and the value of the first differential at the instant of occlusion ($t \equiv o$, i.e., the tangent to the volume curve at this point) would measure the rate of blood flow at the moment of venous occlusion. A practical application of this can be obtained by direct extrapolation of the graph derived by drawing tangents to the volume curve at several points and plotting their values against time. Linear or logarithmic plots of these values may yield a straight line (depending upon the order of the equation of the volume curve) which may be extrapolated to zero time. Should the rate of blood flow at zero time be found to vary significantly from the average rate as usually derived, the latter could not be taken to indicate the rate of flow accurately.

This was actually tested on figures published by Burton,[26] which were derived with an adequate recording system. Extrapolated curves were made of various plottings of the first differential, derived graphically by constructing tangents at various points in time. It was found that the extrapolated rates of blood flow so derived were from 20 to 40 per cent greater than the average estimated rates in these cases. Since the zero rate of blood flow is the more constant, and the factors determining the distensibility of the limb are the more variable, it would appear desirable to obtain the extrapolated blood flow, particularly when the method used is the limiting factor in the accuracy of the study.

A Consideration of the Placement of the Collecting Cuff and Its Inflation.—Inflation of the collecting cuff causes compression and distortion of the limb in its immediate neighborhood. The artifact introduced by the local limb distortion has led many workers to recommend placing the collecting cuff at a definite distance proximal to the recording plethysmograph.[17, 20] Others have, instead, separated the collecting cuff and plethysmograph by an intervening joint,[16, 18, 27] as a matter of convenience, or by an unstated distance. Since the volume increase occurs in all parts distal to the collecting cuff, the change in volume recorded by the plethysmograph when the cuff is at a distance from it represents only a portion of the inflow, and not necessarily a constant portion (Fig. 3). Although this has been noted,[18] and workers in dealing with forearm flow have realized the error of assuming that the segment distal to the plethysmograph increased in volume by an amount equal to its arterial supply,[16, 27] insufficient attention has been directed to this obvious source of error.

A series of experiments was undertaken to evaluate the significance of this factor, as well as to throw some light on the nature of the initial artifact which appears when the collecting cuff is inflated.

As a first step, a wide, leather-backed cuff was placed on the mid-thigh for the purpose of occluding the arterial inflow. When this cuff was abruptly inflated to a pressure of 250 to 350 mm. Hg., a slow increase in the recorded plethysmographic volume appeared (Fig. 4*d*

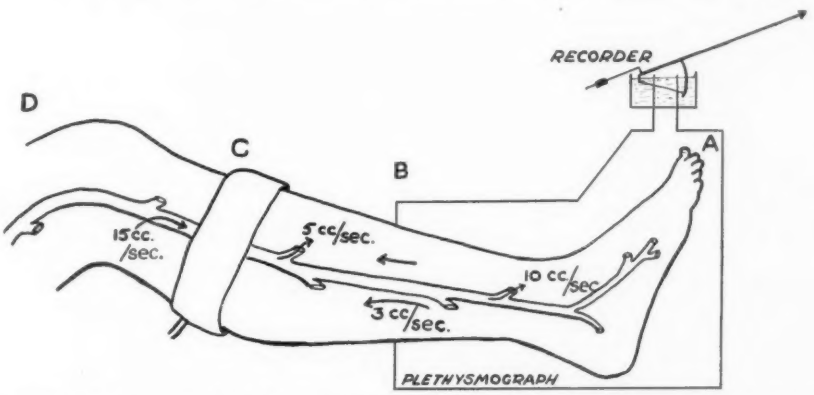


Fig. 3.—Diagram to show the possibly unequal distribution of flow in the limb distal to an occluding cuff, between the portions of the limb within and without the plethysmograph. In this diagram the arterial supply to the limb *ABCD* is assumed to be such that 15 c.c./sec. pass into segment *CBA* below the pneumatic cuff, placed at *C*. Of this, it is assumed that ⅓ is distributed to segment *CB*, and ⅔ to segment *BA*, enclosed in a recording plethysmograph. When cuff *C* is inflated, obstructing the venous return, the segment *CBA* will increase in volume. Only the volume increase of segment *BA* will be recorded by the plethysmograph, which should indicate an initial rise of 10 c.c./sec. However, there is nothing to prevent some redistribution of the 15 c.c./sec. entering *CBA*, between *CB* and *BA*. For example, if 3 c.c. are transferred to *CB* in the first second, the plethysmograph would erroneously indicate a flow of 7 c.c./sec. A similar error would occur if the plethysmograph were arranged so that *CB* were in it, and *BA* outside of it. In short, redistribution of flow necessitates the measurement of the volume changes of all tissues receiving blood distal to *C*.

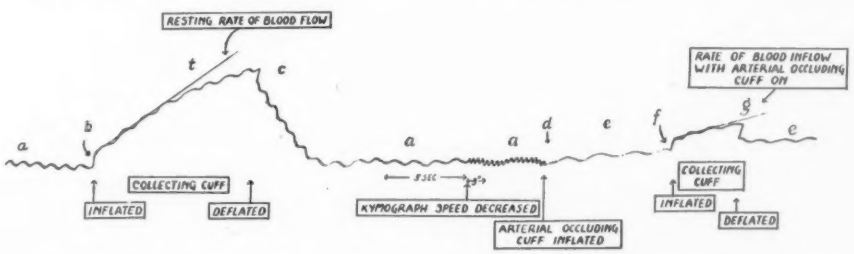


Fig. 4.—A record of limb volume, showing pulse and respiratory variations (*a*), the artifact (*b*) and volume increase obtained when collecting cuff (see Fig. 1) is inflated, with tangent (*t*) representing determination of blood flow, the artifact and volume decrease (*c*) on release of pressure in collecting cuff; abolition of pulsatile variations (*e*) when a cuff on the thigh (see Fig. 1) is inflated at (*d*) to a pressure of 250 to 300 mm. Hg for the purpose of occluding arterial inflow, and, finally, the collecting cuff artifact (*f*) after subsequent inflation of collecting cuff, and the tangent (*g*) giving the rate of "blood flow" which occurs even when the arterial occluding cuff is inflated. Discussed in text.

and *e*). The increase in volume subsequent to arterial occlusion *alone* was relatively large for thirty seconds, and then became smaller and linear over the observed six minutes. This might represent blood redistribution between the part of the limb inside and outside the plethysmograph, or, more likely, as Lewis and Grant[29] suggested, it might represent continuing blood entry into the leg despite the arterial occlusion. The quantity of this persisting flow to the enclosed portion of the limb

ought to be ascertainable by applying the collecting cuff *at* the plethysmograph. When the arterial occlusion was maintained, inflation of the collecting cuff to 50 mm. Hg produced the same initial artifact (Fig. 4*f*) as when no arterial occlusion was present (*b*). This was followed by a continuous increase in recorded volume (*e*) which was greater than before the collecting cuff inflation (*g*). The initial artifact was the result, in part at least, of distortion of the limb by the collecting cuff inflation, which displaced volume within the plethysmograph. Experiments showed (Fig. 5) that this artifact varies in an approximately linear fashion with the applied collecting cuff pressure. The magnitude at any pressure showed individual variations in different experiments, e.g., it varied from 2 to 5 c.c. at 75 mm. Hg.

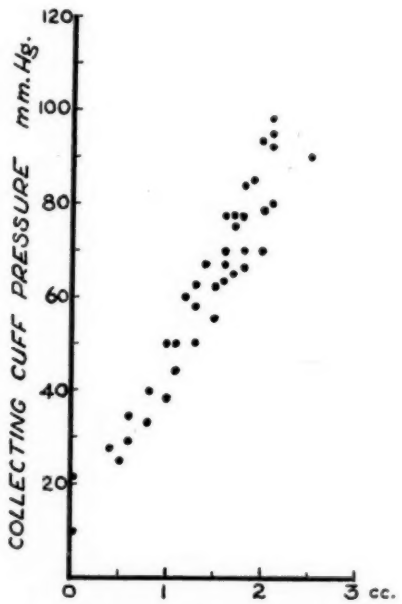


Fig. 5.—Magnitude of initial displacement artifact after inflation to various levels of the collecting cuff when it is placed at plethysmograph (see Fig. 1), carried out after the artery was occluded at mid-thigh by the arterial occluding cuff (see Fig. 1).

This initial artifact decreased when the collecting cuff was applied at a distance from the plethysmograph; in one experiment the relation was 6½:3:1½ at distances of 0, 4, and 8 cm., respectively, but, in another, the artifact was the same at a distance of 8 cm. from the plethysmograph as at 0 cm. distance, and both were greater than at a distance of 4 cm.

The continuous increase in volume after the initial artifact, which was observed when the collecting cuff was inflated with the arterial inflow occluded by a mid-thigh cuff (Fig. 4*g*), may have been due to (a) a secondary, slow component of the initial artifact caused by delay in the

readjustment of the tissues after the application of the collecting cuff, or (b) to flow via bone or other unoccluded arteries.[23]

The rate of this continuous increase in volume decreased progressively more than it did over the same period when the venous cuff was not inflated. This suggested that filling of the limb acted as an impediment to further flow, and so favored the view that this secondary volume change is due, in part at least, to flow via bone or other unoccluded arteries. After the first sixty to seventy seconds of this secondary volume change, this appeared to be the only factor involved. Thus, in the three sets of experiments in which an analysis was made, no definite variation in the rate of volume change occurred with the pressure level existing in the collecting cuff; the rate was approximately the same in all three. This was true also in the four sets of experiments in which the cuff-plethysmograph distance was varied. The amount of volume change was not the same in all subjects or at all levels of occluding pressure, but varied from 0.0 c.c. to 1.0 c.c./min./100 c.c. of limb volume.

The changes in the first part (the first sixty to seventy seconds) of the secondary volume increase suggested that an artifact was involved in causing the limb volume to vary at this time. Thus, the volume change in the first seventy seconds was found to vary with the pressure level in the collecting cuff, and the volume change appeared to vary in a "cyclic" fashion with the distance of the collecting cuff from the plethysmograph.

These results suggest that, after the application of the collecting cuff, an initial, large artifact occurs which varies with the applied pressure and the distance between cuff and plethysmograph. The amount is a function of the applied pressure, but cannot be accurately related to cuff-plethysmograph distance. It is attributed primarily to the displacement of the tissues by cuff application. The primary artifact is followed by a secondary artifact, lasting sixty to seventy seconds, which may be due to continuation of the tissue displacement or to overdamping of the recorder. (The latter can be eliminated by approximating critical damping in the recorder.) In addition, the results show that it is *not* possible to eliminate all the arterial inflow by use of a mid-thigh arterial cuff, even when the pressure is elevated well above the systolic pressure. This is because vessels within bones and perhaps in other localities cannot be occluded. This latter fact does not interfere with simple measurements of blood flow in plethysmographic studies, but the primary and secondary artifacts are of prime importance. Since it is not easy, according to our experience, to eliminate these artifacts by removing the collecting cuff from the plethysmograph, it was deemed desirable to keep the collecting cuff at the plethysmograph, where the magnitude of the primary and secondary artifacts is more predictable, and this practice is recommended, especially because no consideration need then be given to the flow partition between that part of the limb below the collecting cuff inside the plethysmograph and that outside it.

The Plethysmograph and Volume Recorder.—The plethysmograph should be light in weight, rigid, chemically inert, and insulated or jacketed. Its shape and size should, as a rule, be such as to keep the volume of the plethysmograph as small as possible, and yet large enough to accommodate the largest limb to be studied.

Ideally, a gas-containing plethysmograph which can be maintained under controlled conditions of temperature, humidity, and initial volume would least disturb normal conditions; air is the gas generally employed. An air-containing plethysmograph would require a true volume recorder, and no ideal recorder, independent of pressure changes, has yet been developed. The air-filled system would decrease the sensitivity of recorders now available, and increase the time lag in the recording. There are no published studies bearing on the effects of local humidity changes in such air-filled plethysmographs, particularly thermal effects caused by the evaporation or condensation of moisture. These effects could be minimized by having the air saturated with moisture. A more practical objection to air-containing instruments is the large temperature coefficient of expansion of gas; as a result, significant volume changes in the plethysmograph can be caused by slight temperature changes. Thus, a change of 0.1° C. at 27° C. and at atmospheric pressure would increase the volume of each liter in the plethysmograph by 0.33 c.c. Since in limb plethysmographs the air space is several liters, the magnitude of gas expansion and contraction caused by slight differences in temperature may produce a significant error. Moreover, the measurement of blood flow requires stoppage of the venous outflow, and this accumulation of blood in the limb will tend to dissipate more heat from the limb to the surrounding air at a time when constancy of temperature is most essential. Similar changes will occur when the rate of blood flow is altered and when the environmental temperature is altered—both common occurrences.

Fluid, in certain respects, is more convenient to use in the plethysmograph than air. It is virtually incompressible and thus gives rapid transmission of volume changes; it has a small coefficient of thermal expansion, and, in the case of water, a small coefficient of heat conduction. It is also easier to detect leakage of fluid than of gas. However, the use of fluid places the limb in an abnormal environment which prevents evaporation and physically may alter the response of the skin vessels. It also has the disadvantage of imposing hydrostatic pressure upon the limb, the approximate mean value of which is half the depth of immersion, although the effective mean value may be higher if the greater part of the vascular bed is more deeply immersed; these factors may alter blood flow relationships.[30] Another disadvantage of a fluid-filled plethysmograph is the restriction imposed on the position of the limb. It is usually desirable to have the entrance of the part into the plethysmograph at a region which is subjected to little hydrostatic pressure, so that an adequate seal may be effected without producing

constriction of the limb. Finally, in utilizing a fluid-filled plethysmograph—completely or almost completely filled—a large pressure change may accompany the volume changes unless care is taken (a) to adjust the fluid level so that no increase in its height occurs, and (b) to employ a so-called volume type of recorder, i.e., one with large available space moving under little pressure differential. The disadvantages of an appreciable pressure change are that (a) it causes leaks around the entrance seal because this should not be too tight, and (b) it causes an increase in pressure upon the limb, thereby opposing the arterial inflow.[30]

It is apparent from this discussion that the errors and limits of each individual plethysmograph should be ascertained in order to estimate its accuracy and constancy of performance.

Not only the plethysmograph, but the volume recorder, is important with respect to accuracy and constancy of observation. Most of the earlier workers used a modification of the Brodie bellows because of its relative sensitivity and small mass. The particular inaccuracy introduced by such a bellows is that, even if it is prefolded so that it will fold and unfold in a predictable fashion, which is usually not the case with a small bellows, the distortability of the Cargile membrane or goat skin will not permit constancy of calibration. The Brodie bellows, like all types of so-called volume recorders, is activated by pressure changes sufficient to overcome the effective resistance to motion or change of motion, i.e., its inertia. Another disadvantage of the Brodie bellows is that gravity operates to aid motion in one direction and hinders it in the opposite direction. Counterbalanced spirometers[31] avoid this last disadvantage, although they are usually counterbalanced in only one position.

The usual types of recording instruments are so constructed that they are suitable only for relatively slow frequencies; they cannot accurately portray the pulsatory variations during the heart cycle, and each should be tested to ascertain its suitability for measurements of mean flow. For pulsatory flow, a recorder which has a higher natural vibration frequency and is ideally damped is required. The frictional resistance of the writing point and the effective mass of the writing lever must be included in evaluating the characteristics of any volume recorder. Optical recording would eliminate this. Electrical or radio amplifying recorders also require examination from the foregoing standpoint to establish their accuracy.

A further source of error arises from the arcing of the writing lever on the recording paper, for the writing levers of most volume recorders operate from a fulcrum. Thus the ordinates (volume change) are not vertical, but curvilinear, whereas the abscissae (time) are horizontal. The curvilinear ordinates introduce parallax (Fig. 6), and also do not permit accurate construction of tangents which can only be drawn in a Cartesian system of rectilinear coordinates. Hence, the curvilinear

character of the ordinates must not be overlooked, and the graph cannot be considered as rectilinear in construction.

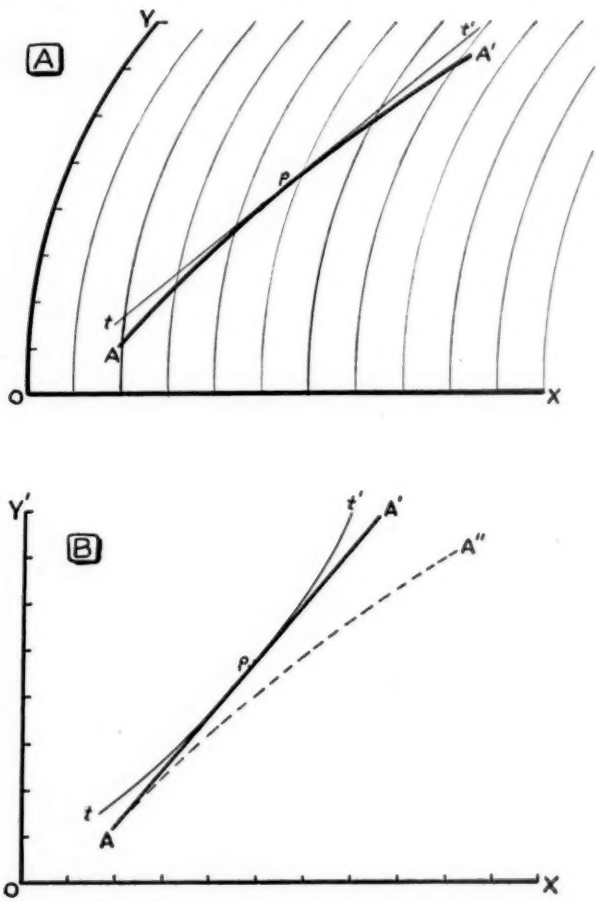


Fig. 6.—Diagram to show the error of the tangent in curvilinear coordinates. In *A*, *OX* and *OY* are the coordinates of limb volume records, such as were used in these studies. *OX* = time and is rectilinear; *OY* = volume and is curvilinear. *AA'* represents the equation of a straight line, which, when plotted on these coordinates, becomes a curve. The true tangent to *AA'* is *AA'* itself. If a "tangent line" *tpt'* is applied to curve *AA'* at *p*, this is in reality a curve, and therefore is not a true tangent. In *B*, representing rectilinear coordinates, *OY'* and *OX* have otherwise the same meaning as in drawing *A*; the line *AA'* is correctly plotted as a straight line; and *tpt'*, its supposed "tangent," when plotted correctly here, is a curve. *AA''* represents the erroneous curve representing the line *AA'*, which is produced in a curvilinear system, if the curvilinear system is assumed to be rectilinear (i.e., if parallax is neglected). Discussed in text.

Several other considerations have been given considerable attention by other workers. An important factor, of course, is the relation of the instrument to the level of the heart.[20, 29] Another is the possible limitation of the method for limbs with an impaired circulation, a collateral circulation, or both.[36] By convention, the unit for expressing flow[20] is volume change in c.c./min./100 c.c. of limb volume, or c.c./min. The minimal time between successive measurements was ascertained; it

was found that measurements can be made every ten seconds without influencing the results.

The Final Assembly Used in This Study.—After the foregoing analysis of the principles of proper plethysmographic recording was made, the following assembly was utilized because it was a practical, convenient arrangement in which errors could be obviated or known.

For the foot-leg we have adapted the large, double-walled plethysmograph of Abramson, et al.[17] This, as designed for use with water, required that the leg be dependent. Calibrations for volume and rate of change in volume, when the instrument contained air, as well as comparative experiments done with water and with air, revealed no significant difference, and in all subsequent studies it was used as an air-containing plethysmograph, usually with the limb within 10 cm. of the heart level, and the patient in a comfortable supine position, with the leg horizontal. Circulation of air for heating was provided by a detachable, thermostatically controlled hot-air blower. The plethysmograph volume was 6,500 c.c. A tube, 2.5 cm. in diameter and 20 cm. in length, connected the spirometer to the plethysmograph.

For the recording instrument, small spirometers of the Gad type were constructed; they were of several capacities, up to 60 c.c., and sizes, up to 3.5 by 5.8 cm., and weights (including counterbalance), up to 12 Gm. Each was made of three pieces of x-ray film, cemented together by a solution of x-ray film in acetone (one piece may be used). To this was fastened a metal-wire fulcrum, a counterbalancing arm, and an aluminum recording arm with an effective radius of 39 cm., on which was cemented a conical celluloid pen such as is used for barographic recording, The capacity of this pen was increased and adapted for vertical writing by cementing upon it a small, truncated, celluloid or cellophane cylinder. The recorder pivoted on notches in the edge of a container 8 by 5.5 by 5 cm., which contained a mixture of glycerine and water. A 2.5 cm. tube extended through the bottom, reaching above the fluid level. The proportions of glycerine and water were chosen to damp the instrument approximately critically. The damping was produced by the amount of surface of the spirometer in contact with the liquid, the nature of the liquid, friction of the pivotal bearings, friction at the writing point, the flexibility of the writing arm, and the position of the counterbalance. The surface relation of spirometer to fluid was large and could be made variable. Smaller recorders with proportionately more surface may be overdamped unless less viscous liquids are used. This could be adjusted by using varying proportions of alcohol, glycerine, and water; the specific gravity in this way could be varied from 0.8 to 1.26, and the viscosity, from 10 to 8,700 η. In glycerine mixtures as we have used them, the water may be replaced as it evaporates, in order to keep the composition roughly the same. Freeman and Zeller[31] have used a similar volume recorder in mineral oil, and Kolin[32] has suggested glycerine to effect aperiodic damping.

In the arrangement used by us, a pressure difference of less than 0.02 mm. Hg will set the spirometer in motion.

The frequency response characteristics for volume and rate of volume change were ascertained for the recorder alone and for the plethysmograph and recorder, by attaching, in a closed system, without valves, a cylinder-piston pump driven from a circular cam, so that the volume increase and decrease that were produced were in the form of a sine wave. The percentage of error in recording volume changes was ascertained for various volumes at the various frequencies of the pump (Fig. 7*A*). This error is the same as that which occurs in recording the average rate of volume change at these stroke frequencies for the several magnitudes of stroke volume. In addition, recorded maximum rates of volume change were obtained by drawing the maximal tangents to these curves, and these were compared to the theoretical *maximal* rate of volume change for the various volumes and frequencies. The percentage $\left(\frac{\text{maximum recorded rate}}{\text{maximum theoretical rate}} \times 100\right)$ so obtained is a more significant indication of the over-all accuracy of the instrument in recording rate of change over the various ranges of volume and over the various ranges of rates of change in volume. The values indicating this accuracy were plotted according to frequency of the pump (Fig. 7*B*) and according to the maximum rate of change of volume (Fig. 7*C*). These plots include not only the error of the instrument, but also the error of calculating the results.

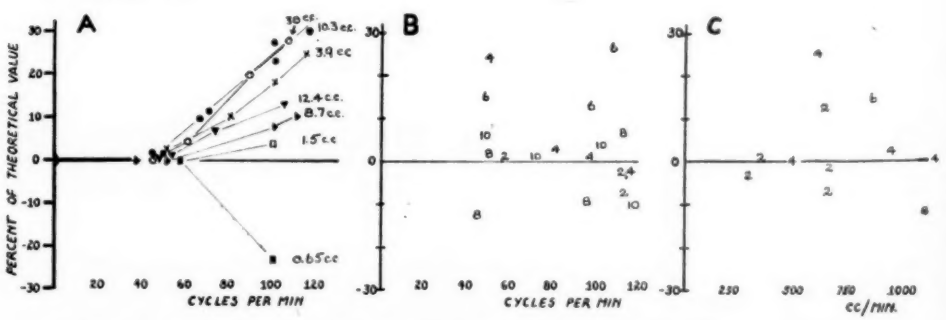


Fig. 7.—*A* shows the variation in accuracy of recording volume as the frequency of the pump is changed at the different stroke volumes indicated. *B* shows the variation in accuracy of recording (and computing) maximal rate of change in volume as the frequency of "sine wave" pump is changed. The figures indicated at points on graph represent stroke volume in cubic centimeters. If V is the stroke volume of the pump and f is the cycle length of the pump, the tangent representing the theoretical maximum rate of change in volume = πVf. *C* shows the variation in accuracy of volume recorder in recording (and computing) maximal rate of change in volume. The values of *A*, calculated in c.c./min., are plotted against the theoretical maximal rate of volume change.

Such a determination of the characteristics of a volume recorder are especially important when one is attempting to measure the rate of change in volume. Thus, if +10 c.c. is recorded with an error of ±10 per cent as +10 c.c. ± 1 c.c., and the increase occurring within 0.1 second is recorded only after 0.2 second, the rate of change in volume recorded

is 50 c.c./sec. ± 5 c.c., but the actual rate is 100 c.c./sec., and the true error of recording is not the error of the volume recording but the combined errors of volume and rate recording. In the example given this is actually 45 to 55 per cent.

After the characteristics of the instrument were known, certain precautions were essential in regard to the placement of the limb in the plethysmograph. The limb was supported by placing a sponge beneath the heel and sandbags below the knee (Fig. 1). Airtight, nonconstricting closure was obtained by means of a sheet of rubber, 1 mm. thick, in which an ovoid hole was cut to the appropriate size for the desired height on the leg. Rubber cement was applied about the leg and along the edge of the rubber sheet in a band 0.5 cm. wide, and the sheet was then everted toward the toes and attached as a cuff to the leg. After the cement had dried and the attachment of the sheet had become secure, the sheet was slightly stretched and fastened over the opening of the plethysmograph with a metal ring. Thus, a closure diaphragm was made which, by proper selection of size of opening and tension on the rubber, would not exert significant pressure upon the limb. In fact, care was taken to avoid traction on the skin. Once the diaphragm had been fitted in place and tested for leaks, a plaster of paris paste, not quite thin enough to pour, was prepared and smeared over the outside of the rubber to make a diaphragm 2 to 4 mm. in thickness. This set in two or three minutes, forming a light, rigid closure. This method is similar to that of Wright and Phelps,[18] who used Unna's paste instead of a rubber sheet. The modification we employed prevents leaks more effectively; the disadvantage is that it permits but slight movements of the leg.

When the apparatus was ready for use, it was again tested for leaks. This was conveniently accomplished by deliberately setting the spirometer recorder off balance, first in one direction and then in the other; leaks were shown by drifts of the recorder. When leaks were absent, the collecting cuff, 5 cm. in width, was placed about the leg close to the plaster seal. A 16 cm., leather-backed cuff had been previously strapped smoothly but loosely about the thigh for use as an arterial occluding cuff in studies on reactive hyperemia. Each cuff was connected to a pressure tank and manometer under suitable pressure, with a valve arrangement to permit abrupt inflation and deflation of the cuffs. The arterial occluding cuff was inflated from a 20 liter metal drum, and the proper pressure level in it was set with a pump. The venous occluding cuff was inflated from two such drums, and the pressure level was set in them by hand with a rubber sphygmomanometer bulb. A damped mercury manometer, carrying a float and pen writer, was connected to the collecting cuff to record the time and speed of inflation and deflation, and the duration and pressure level of inflation.

All tracings are recorded in ink upon a vertical paper, 30 cm. wide. This is driven from a continuous roll by a friction drive, operated by a

synchronous motor with six geared forward speeds.* The paper speed is constant within 1 per cent over the range of speeds available, namely, 9.5 to 1,730 mm./minute. Time and signal markings are recorded by continuous feed pens on the signal magnets. Time impulses at ⅕ to 5 seconds intervals are delivered from a specially built A.C. timer.* After the subject had been at rest for thirty minutes, tracings were made. Normally, pulsations were noted, and, with the kymograph running, the collecting cuff was inflated abruptly. After a curve of sufficient duration was obtained, the cuff was deflated. Each such recording occupied a few seconds and could be repeated quickly. Actual sections of a record are shown in Fig. 8.

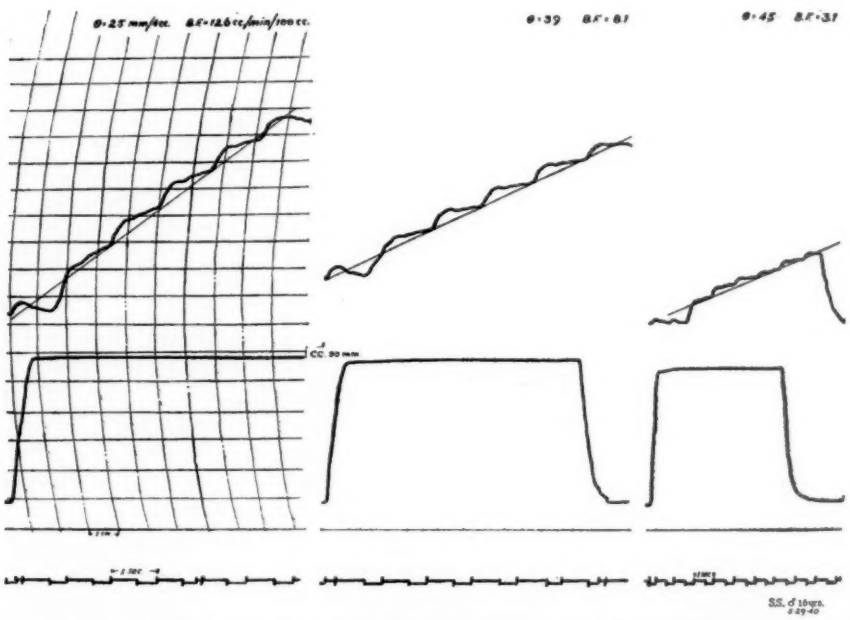


Fig. 8.—Sections of a kymographic record, showing, from above down, (1) volume record after inflation of collecting cuff and the tangent indicating rate of blood flow, (2) record of pressure within collecting cuff, (3) base line, (4) time in seconds. Three successive determinations are shown; in the first the curvilinear time lines 1 cm. apart, and the horizontal volume lines, 2 c.c. apart, are drawn in. In the upper right hand corner of each graph the tangent value and its corresponding blood flow are indicated. This figure is part of a series of curves taken during subsidence of reactive hyperemia. It illustrates the procedure of slowing the rate of the drum (3rd graph) to make the tangent approach 45° to simplify calculation of blood flow. Note the slight initial artifact on inflating the collecting cuff, and the contour of the individual pulsations, which bear a superficial resemblance to a pulse wave contour. The parallax between the volume record and the intra-cuff pressure record are deliberate, to permit full excursions of both writing points.

In each single experiment, requiring one to two and one-half hours, from ten to fifty resting flows were obtained as controls. In the experiments with reactive hyperemia, repeated arterial occlusions were produced for selected periods of time. Flows were measured at the moment of release of the occlusion, as was done by Lewis and Grant,[29] by inflat-

*Designed and constructed by Mr. S. F. Gaddas.

ing the collecting cuff just before release of the arterial cuff,* and this was followed by making measurements every ten to fifteen seconds, or less frequently, as required, until resting values were reached. In this way the curve of change in flow was ascertained. If only a single observation is made (e.g., at ten seconds after release[27, 33]), this may not depict the maximal flow, or even a constant proportion of it.

In the experiments with elevated bath temperatures, heating was interrupted during the actual flow measurement. Under these conditions, long-time volume changes were not considered reliable. Absence of volume changes over the period of measurement (three to five seconds) was tested by demonstrating that there was no change in the base line during an equivalent interval preceding or succeeding this period. In the instances in which no marked change in temperature occurred, relative "basal" changes in limb volume were noted before the inflation of the collecting cuff.

Movements of the limb and coughing and speaking are detectable by irregularities in the tracing. Adequacy of arterial occlusion was shown by (a) abolition of pulsations and (b) absence of blood flow on applying the collecting cuff. Room and boot temperatures were taken. At the conclusion of each experiment the leg volume was measured to within 10 c.c. by overflow displacement of water, immersing the dependent leg to the level of the rubber and plaster seal. (This gives the volume of leg partially filled with blood.)

Manner and Accuracy of Measuring the Recorded Volume Changes, and the Rate of Change.—The record was measured by placing it under two celluloid sheets on a drawing board. Upon one there are a horizontal base line (to which the base line of the tracing is matched) and a parallel calibration chart obtained from calibration of the empty apparatus. Upon the other celluloid sheet there are parallel, vertically oriented, curvilinear ordinates 5 mm. apart, drawn from a radius equal to that of the writing arm of the recorder. All points upon each curvilinear line, when properly oriented to the horizontal base line, therefore represent the same moment in time. The interval included between these lines depends, of course, upon the speed of the recording paper. With these two celluloid sheets superimposed, the volume change and time can be read directly, as from any rectilinear graph.

Inasmuch as a pressure differential of less than 0.02 mm. Hg sets and maintains the spirometer in motion, it can be considered essentially as a volume recorder. Since the closure of the plethysmograph when in use is essentially rigid, all volume changes are transmitted to the recorder, and therefore the calibration of the empty instrument is suitable for use. A check calibration for several points of the scale was made

*Sometimes an artifact in volume was produced here by movement of the leg on release of the occluding cuff. This could often be minimized by placing the cuff so that it would not come against any support when inflated, or it could be avoided by measuring blood flow in the usual manner one to two seconds after the release of the occluding cuff; the more predictable artifact of the collecting cuff was present in this case.

in every case with the limb in place, usually with the artery occluded. For any error (caused by warping of the spirometer) the proportionate correction factor was inserted in the calculation.

It is incorrect to apply the theory of tangents to a curvilinear system in obtaining rate of volume change. The line tangent to our recorded curve would, in this system, be a curve, not a straight line, and it would vary with the angle from the vertical which the curvilinear line makes at the point to be measured. An attempt was made to overcome this error. We selected a fixed unit of volume change (4 c.c.) and ascertained the time (in minutes) required for this volume increase on a "tangent" drawn at the appropriate point. This was done to keep the error of curvature of the volume ordinates more nearly constant than could be done by ascertaining the volume change for a fixed time period.

Thus, rate of blood flow in cubic centimeters per minute equals $\frac{4}{t}$

The "tangent" line was drawn to fit the initial second or two of the curve. This was taken after the artifact was inscribed (usually after 0.2 second), and, when after vibrations were present, a mean curve was selected.

The calculation was actually done as follows:

$$\text{Rate of blood flow (in c.c./min.)} = \frac{4}{t} \times R$$

where $R = \frac{\text{actual volume calibration}}{\text{recorded volume calibration,}}$ and t = time in minutes.

Time, t, is expressed as the distance θ (in mm.), traveled at the set speeds 1 to 6 of the kymograph.

$$t \text{ (in min.)} = \frac{\theta}{S_n}$$

where S_n represents the paper speed (in mm./min.).

Rate of blood flow (in c.c./min./100 c.c. limb volume) =

$$\frac{4\ R\ S_n\ 100}{V\ \theta} = \left[\frac{400\ R\ S}{V}\right]\frac{1}{\theta}$$

where V = volume of limb (in c.c.).

The expression $\frac{400\ RS_n}{V}$ is a constant (F_n) for each experiment, selecting for S_n the speed $S_{1\text{-}6}$. It is most convenient for calculation to select a speed so that the tangent will have an angle near 45° (Fig. 8). With this factor (F_n) as a slide rule setting, flow may be calculated for each tangent distance θ in a single direct operation.

In short, blood flow = $\frac{F_n}{\theta}$ in c.c./min./100 c.c. limb volume.

Observations on Resting and Maximal Blood Flow in the Legs of Normal Subjects.—With the method described, nineteen experiments were performed on seventeen normal subjects. In six patients the resting blood flow was measured with the leg dependent, and, in thirteen, with the leg horizontal. In the former the resting flow was 0.6 to 7.0 cc./

min./100 c.c. limb volume, and, in the latter, 0.5 to 6.0 c.c./min./100 c.c. limb volume. These observations are summarized in Fig. 9; the subjects in each series are arranged according to age.

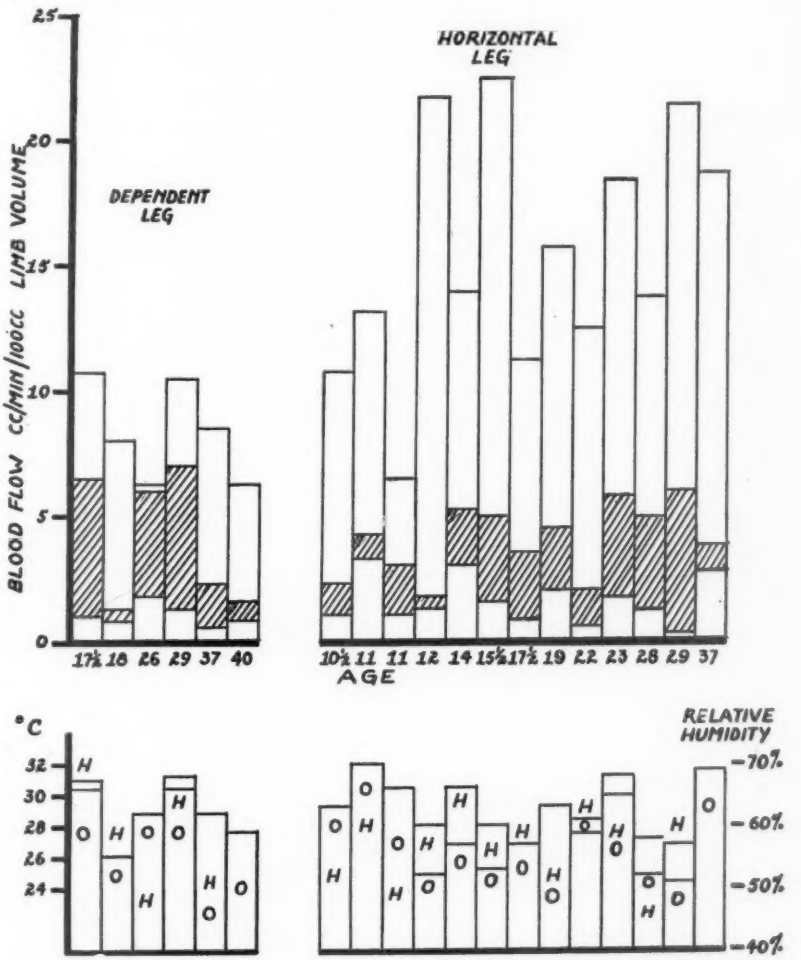


Fig. 9.—Blood flow in dependent and in horizontal position of foot-leg of normal subjects, arranged according to age. Maximum flow during reactive hyperemia shown by height of columns. Resting flow range shown by cross-hatching. Temperature in plethysmograph is shown by single or parallel horizontal lines; room temperature, by open circles; and relative humidity, by *H*.

In each of these experiments reactive hyperemia was induced by producing arterial occlusion for four to twelve minutes. The maximum flow on release was found to be 6.4 to 10.8 c.c./min./100 c.c. limb volume in the experiments with the leg dependent and 6.3 to 22.5 c.c./min./100 c.c. limb volume with the limb horizontal (Fig. 9). Such differences were seen when the flow with reactive hyperemia was measured on the same subject on different days with the leg horizontal and dependent. Typical examples of the time course of reactive hyperemia are shown in Fig. 10.

Comparative blood flow measurements on the same patient were made with the leg dependent, using the apparatus as an air and a fluid plethysmograph. The resting flow values in the air plethysmograph were 1.8 to 7.0 c.c./min./100 c.c. limb volume, and in the fluid plethysmograph they were 1.3 to 4.0 c.c./min./100 c.c. limb volume. The maximum flows during reactive hyperemia were, respectively, 9.6 and 10.6 c.c./min./100 c.c. limb volume for the air- and for the fluid-containing plethysmographs.

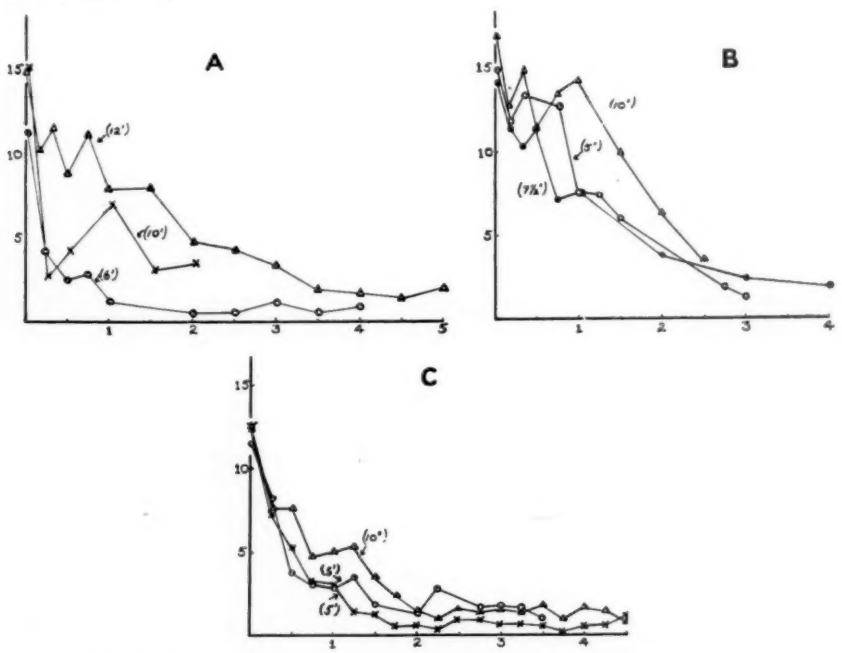


Fig. 10.—Time course of rate of blood flow in foot and leg after release of arterial occlusion, showing extent and subsidence of reactive hyperemia in three normal subjects. Abscissae indicate time in minutes; zero time is the moment of release of arterial occlusion; ordinates indicate blood flow in c.c./min./100 c.c. limb volume. The duration, in minutes, of arterial occlusion preceding each curve is shown in parentheses.

In a number of cases comparative measurements were made of the maximum flow during reactive hyperemia after arterial occlusion with the maximum flow when the leg was warmed to 43° C. for thirty minutes or longer.* In one case the flow at 43° C. was 7.5 c.c./min./100 c.c. limb volume, as compared to 6.4 c.c./min./100 c.c. limb volume during "reactive hyperemia." In another case (Fig. 11) the maximal flow during reactive hyperemia was 10.8 c.c., on heating it was 8.0 to 13.1 c.c., and on inducing reactive hyperemia in the heated leg it was 10.5 to 14.6 c.c.

Our values for resting and maximal flows in the normal limb in the horizontal position are of the same order as those reported in the litera-

*Some question might be raised as to the comparability of heating a leg in an air bath and a water bath. It has been stated that there is a difference in effectiveness in producing reflex vasodilation.[34] Our maximum of flow in the air-heated limb corresponds fairly well with the results obtained by heating in a water bath.

ture (Fig. 11). Abramson, et al.,[17] reported flows of 1.3 to 6.6 c.c./min./100 c.c. limb volume at 32° C., and 9.9 to 17.2 c.c./min./100 c.c. limb volume at 45° C., and, in another study, 1.4 to 5.5 c.c./min./100 c.c. limb volume at 32° C. and 9.8 to 25.5 c.c./min./100 c.c. limb volume at 45° C.[35] Kunkel and Stead[36] reported maximal flows at 43° C. of 11.1 to 25.9 c.c./min./100 c.c. limb volume. Five minutes of arterial occlusion did not increase the flow in the heated extremity in two patients, whereas in a third the flow increased from 22.9 to 26.4 c.c./min./100 c.c. limb volume. Wright and Phelps[18] reported, for a large volume of leg, a resting flow of 1.8 to 4.2 c.c./min./100 c.c. limb volume, a maximal flow, after heating, of 6.9 to 8.0 c.c./min./100 c.c. limb volume, and, after heat and sacral diathermy, of 11.7 c.c./min./100 c.c. limb volume.

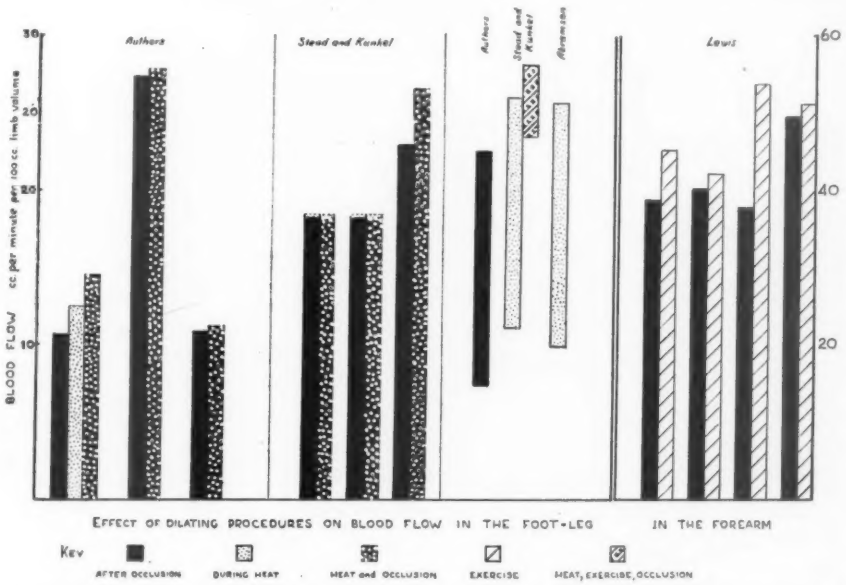


Fig. 11.—Effect of various dilating procedures on blood flow in the foot-leg and in the forearm. Our results were obtained in the present study; see Kunkel and Stead,[36] Abramson et al.,[35] and Lewis and Grant.[29]

In the studies of Killian and Oclassen,[37] the recorded blood flow in the foot at room temperature was 0.9 to 4.2 c.c./min./100 c.c. limb volume, and, after dilatation by local heat and a hot mustard bath, the values were 6.4 to 14.8 and 7.3 to 13.2 c.c./min./100 c.c. of limb volume,* respectively.

Our results also confirm the amply demonstrated observation[1, 9, 20, 31, 37-39] that there is a general correlation of resting flow with local or environmental temperature.

Although there is no precise correlation of limb blood flow with age,[36] the resting flow appeared to be less in the younger subjects of our series. It must be noted, however, that the oldest subject was only 40 years of age.

*Data given, or calculated by approximation from data given.

Our results, which indicate that the maximum flow in the resting dependent limb is less than that in the horizontal limb of the same and of other patients, are in keeping with other evidence that the flow to the dependent limb is reduced.[40, 41] This may be because the cardiac output is less in the sitting than in the lying position[42-46]—although this observation has been questioned[47, 48]—or because of congestion of the dependent vessels[43, 49, 50] and/or a diminution of circulating blood volume.[51]

In the sitting position, hydrostatic pressure up to the height of the blood column (of the order of 50 mm. Hg) is thrown upon the arteries and veins of the limb, and distends them.[50] This is compensated for to some extent by an alteration in the general systemic blood pressure level.[51] The hydrostatic pressure would nevertheless operate to increase intramuscular tension in the dependent leg, to distend the leg and its blood vessels, and thus to increase the cross-section area of the vascular bed. The net effect would be greater resistance to the inflow of blood to the leg, as well as greater opposition to passive or active constriction of the blood vessels of the leg. The pooling of blood in the dependent parts could decrease the venous return, the circulating blood volume, and the cardiac minute output, all of which would further tend to reduce the blood flow. The resting flow could be maintained unchanged by compensatory dilatation, but the existing differences might be indicated by comparing the fully dilated vessels.

Apparently because of the balance and variation of the factors in operation, we were unable to demonstrate a difference of resting flow in the two positions beyond the limits of error of the method, but a difference in flow was demonstrable with the vessels fully dilated by heat or reactive hyperemia (Fig. 9).

Before our results are taken to indicate confirmation of the foregoing concept, it must be ascertainable whether the method is as reliable for the dependent as it is for the horizontal leg. The same conditions which act to reduce blood flow may also limit the validity of the method of measuring blood flow. These factors are elevation in venous pressure and distention of the veins and tissues of the limb. The elevation of the venous pressure caused by dependency of the limb may prevent complete occlusion of the veins when the collecting cuff is applied, and the presence of more distended veins and a more distended leg may make the resistance to further distention greater. In order to rule out these possibilities, the distention and increased venous pressure which occur in the dependent leg were reproduced in the horizontal leg by congesting the limb prior to, or during, the arterial occlusion. This maintained an increased venous pressure but did not interfere with the development of the resultant hyperemia.[29] Under these circumstances, the initial flow was sometimes found to be less (Fig. 12) and the maximum inflow to occur later than in those experiments without venous congestion. The presence of congestion at the start offered resistance to inflow, but, with the release of the arterial obstruction, the conges-

tion was quickly relieved because the venous occlusion was also removed, and the limb volume therefore decreased. As the inflow increased it tended to cause an increase in leg volume, as it did in the uncongested limb, but this increase was delayed or masked by the pre-existing congestion.

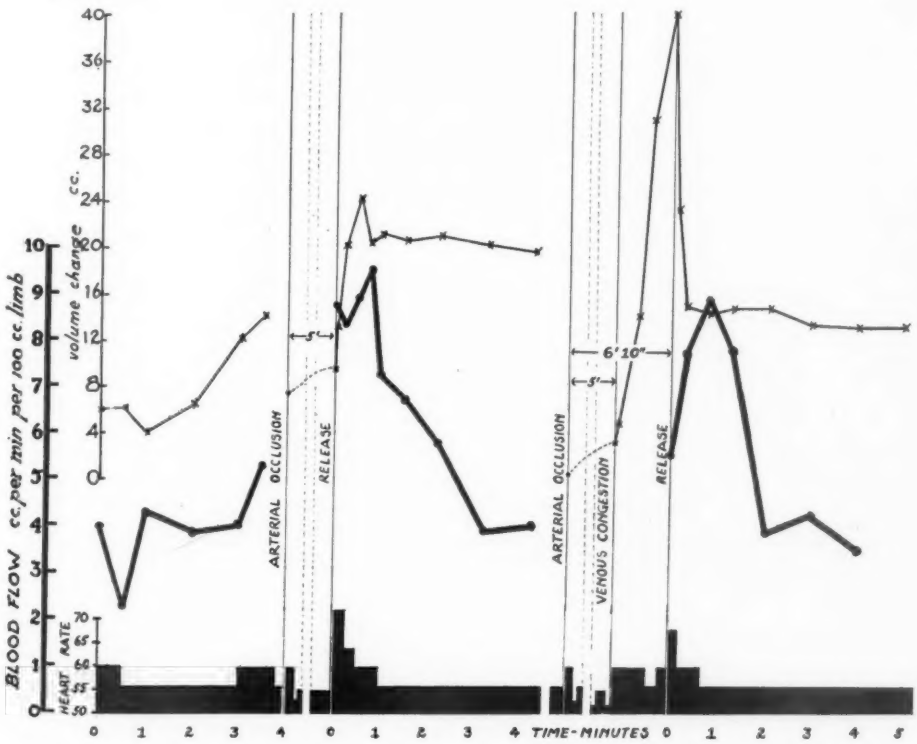


Fig. 12.—Effect of release of arterial occlusions of like duration with and without venous congestion. Blood flow is represented by the heavy line; relative limb volume, by the light line; and heart rate, by blocks.

This alteration of flow as a result of congestion may explain how, in a previously uncongested limb, a temporary decline in blood flow occurred in some instances during reactive hyperemia (Figs. 10 and 12). When the arterial occlusion was released in an uncongested leg, blood entered the leg faster than it could leave, with the result that the leg volume increased (Fig. 12) and the pressure in the small vessels and veins rose.[52] This, in turn, offered resistance to further flow, which might have resulted in a decline in the rate of inflow when the limb volume was at a maximum. On the other hand, the congestion and rise of venous pressure themselves led to acceleration of outflow, thus relieving the hindrance to inflow; at the same time, the pulse acceleration resulting from the release of arterial occlusion (Fig. 12) indicated a temporary increase in cardiac output which tended to increase inflow above normal. These two factors, therefore, caused the initial decline to be temporary, and therefore to appear as a notch on the curve of

flow (Figs. 10 and 12). Intermediate degrees of congestion or venous pressure elevation may be expected to effect similar trends. The increased venous pressure produced by deliberate congestion quickly disappeared after release, whereas that in the dependent leg, because of its position, was constant.

It is indicated by these experiments that (a) congestion of a limb, per se, decreases inflow, and this can account for the decreased maximum flow in the dependent limb, and (b) the presence of congestion makes observation by this method less reliable, and therefore more accurate data on resting and maximum flows are to be obtained in the uncongested limb than in the congested one. However, the degrees of venous pressure elevation deliberately produced in the experiments with congestion were much greater than might be expected under ordinary clinical conditions of increased venous pressure. Nevertheless, optimal conditions require low venous, tissue, and environmental pressure, and therefore the use of a horizontal position of the leg near the level of the heart. We do not think that the decreased flow in the dependent leg, the initially low flow in the congested leg after release of arterial occlusion, and the transient decrease in flow in the uncongested leg after release of arterial occlusion are reliably quantitated by our measurements.

It has often been pointed out that maximum flow is a better measure of the vascular status of a part than is "resting flow."[36] The resting flow is determined largely by the amount of vasoconstriction caused by humoral, physical, or neurogenic influences. Most workers have used heat to produce maximal flow. Our selection of reactive hyperemia was deliberate because we were interested, in part, in the study of its mechanism.

Our values for maximal flow in the normal leg-foot in the horizontal position are of the same order of magnitude as those reported by other workers who studied similar subjects, but employed heat to produce maximal flow (Fig. 11). Heat, whether used alone or in combination with reactive hyperemia, gave slightly greater flow than reactive hyperemia alone, both in our experiments and in those reported by others. Other dilating agents have produced no greater flow.[37, 53, 54]

Heat and reactive hyperemia do not operate in an identical manner. In the leg-foot we are dealing with the flow in both skin and muscle. Heating an extremity to 43° C. for thirty or more minutes produces dilatation primarily of the skin vessels.[23] The deeper vessels are not dilated; in fact, muscular vessels may be constricted. Apparently, all the skin vessels participate in this dilatation, viz., A-V shunts,[55] arterioles and venules, probably the arteries, and perhaps the veins. The dilatation involves not only the locally heated vessels, but also the skin vessels throughout the body as a result of a reflex mediated by sympathetic cutaneous nerves.[56, 57] Consequently, there are changes in blood distribution, blood pressure, and cardiac output. The dilatation re-

quires a certain amount of time to reach a steady state and disappears slowly. The function of the circulatory adjustments in this case is temperature regulation. Other functions of the circulation—the transport of metabolites—are not primarily involved. In fact, the dilatation of A-V shunts in the skin may actually decrease the blood flow through the "working" capillaries of the tissues.

The advantages of the use of heat are the tolerance of most subjects to it, the ease of its production, and the fact that it can be maintained to get check readings. The disadvantages consist in the alteration of the normal conditions of the limb, in the time (about one-half hour) required to reach a steady state, in the difficulty of maintaining controlled heating in an air-system plethysmograph, in the intolerance of some patients to it, in the variability of response to it among patients, and the limitation that the dilatation produced is primarily in skin vessels.

On the other hand, during reactive hyperemia after occlusion, the smaller arterioles and the capillaries and venules of the entire extremity are dilated.[23] An increase in heart rate and a change in blood pressure occur.[58] The blood flow of the opposite extremity is, however, not significantly affected. Reactive hyperemia results from anoxia, and the increase in flow is the means by which the oxygen debt is quickly repaid. The advantages of the reactive hyperemia method are that the dilatation is more widely distributed in the limb, observations may be made and repeated with ease and speed, normal rate of flow soon returns, and generalized alterations in circulation do not occur. The disadvantages are occasional pain and discomfort, interference with limb nutrition, and the transient character of the dilated state which is produced.

Increasing the duration of the occlusion resulted in an increase in the maximal flow after release of the occlusion. The relationship between the duration of occlusion and maximum flow is presented graphically in Fig. 13 for our results and for the results published by Lewis and Grant.[29] The maximal flow did not increase proportionately as the duration of occlusion was increased, but approached a limiting value. This limiting maximal flow was obtained by occlusion for ten to fifteen minutes, and indicates that about 80 per cent of the maximal flow may be reached after release of occlusion which has been maintained for five to ten minutes. Shorter and repeated periods of reocclusion, if promptly applied after release of a longer occlusion, also produced a high maximal flow upon release.*

One or more of three factors may impose a limit upon this maximal flow: (a) when the occlusion is maintained beyond the optimum time, constricting factors may limit the effective dilatation; (b) as the occlusion is prolonged, the vessels may reach the maximum extent of their dilatability, both as regards degree and number of vessels; and (c) it

*Contrary conclusions were drawn from work on anesthetized animals,[59] but they were based on limb volume observations, not on blood flow measurements.

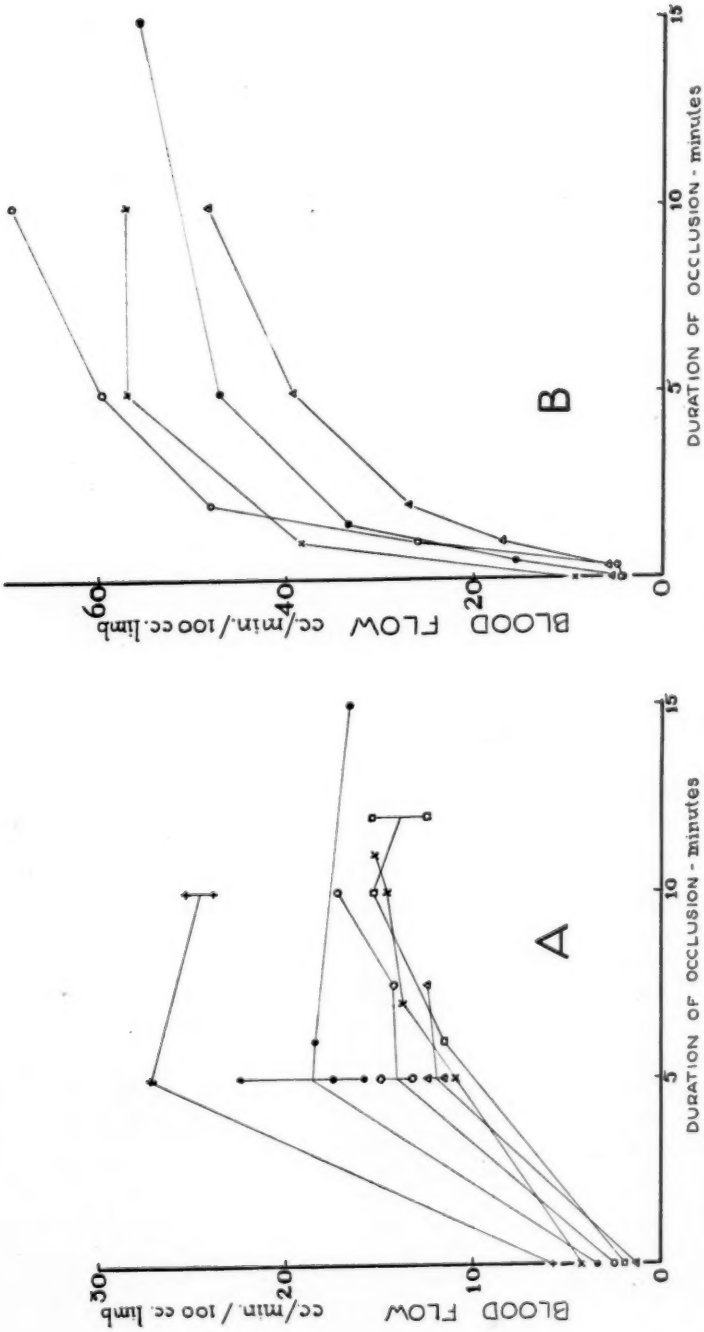


Fig. 13.—In *A* are plotted our results on the relation of maximum flow in the foot-leg after release of arterial occlusion to the duration of this occlusion. In *B* are plotted the data of Lewis and Grant [29] on the relation of blood flow in the forearm at the moment of release of arterial occlusion to the duration of such occlusion.

should be recognized that, as the dilatation is increased beyond a certain point, the resistance offered by the larger vessels, or at least by vessels not participating in the dilatation, becomes proportionately greater, until the limit of flow may be determined primarily by the caliber of these vessels, rather than by those which are being dilated.

As regards the use of other dilator agents, the experiments of Wright and Phelps[18] are applicable. Maximum flows as a result of using heat alone were as great as those obtained by any combination of methods with heat, and were approached only by the values after nerve block. In their studies, sciatic block, spinal anesthesia, diathermy, and reflex and local heat were used. Kunkel and Stead[36] reported that heat plus arterial occlusion, and both plus exercise, resulted in flows in the foot which were little, if any, greater than those produced by heat alone. Applying heat to the forearm[29, 36] did not produce maximal dilatation in this region. This was attributed to the relatively small proportion of skin in the vascular area of the forearm. Arterial occlusion and exercise, or both, yield about the same maximal flow in the forearm.[16, 53, 60*]

This evidence indicates that the maximum flow in the foot-leg is of the same order of magnitude, although produced by diverse means. It is hardly likely that all the peripheral vessels dilate to the same degree under each of these conditions. It is more probable that some other factor limits the maximum rate of flow. This could be the cross-section area of the central arteries. The principle of continuity of flow, which predicts that the amount of flow in one section of a system of tubes equals that in the preceding section when conditions are stabilized, applies here. Under a given driving force (the arterial pressure), there is a limit to the amount of flow which can pass a given point in the central artery, and this might be considerably less than the amount which could pass through the dilated vessels beyond. If this be true, when the resistance in the peripheral vessels falls below this level, the factor determining flow will become the cross-section area of the feeding artery to that region. An analogy may be drawn to a plumbing system in which water flows from a main through an inlet pipe to be distributed to a household. When most of the faucets are closed, the flow from the main to the inlet pipe is determined by the number of open faucets. As more and more are opened, a point may be reached at which the factor limiting flow in the inlet pipe is the cross-section area of the pipe itself. At this point, even if more faucets are opened, no significantly greater flow can occur. Whether or not this happens, and the point at which it occurs, depend upon the relative size of the inlet pipe and the size and number of the faucet openings. To carry the analogy further, when pipe corrosion occurs or scale is deposited in the inlet pipe, the maxi-

*Since a distal occluding cuff about the wrist and ankle is used in measuring forearm and calf flow, it would be desirable to examine the method critically in this instance before accepting the results unreservedly.

mum amount of water that can be drawn per unit of time will be decreased. This concept is of some importance in understanding the usefulness of maximal flow, for it shows that, under certain circumstances, maximum flow may not measure the maximum dilatation of peripheral vessels, but may measure, instead, the cross-section area of the artery to the part. It may explain why maximal flow in the normal leg and foot is obtained by dilating only skin vessels with heat, as well as by dilating all the small vessels with reactive hyperemia. *Variations in maximal flow under different circumstances may therefore mirror changes in systemic pressure (driving force), express changes in peripheral resistance in the small vessels, or indicate alterations in central arterial caliber.* Flow varies directly with pressure and inversely with *total* resistance (in series).

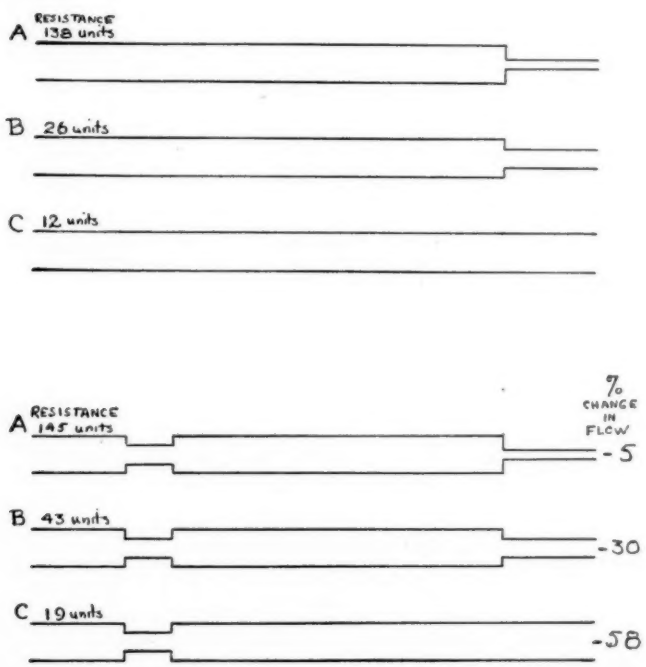


Fig. 14.—Upper set of diagrams represents the same central vessel with three different degrees of peripheral vascular caliber. Lower set of diagrams represents the effect of equal constriction of this central vessel upon the flow through the above three vessel systems. On the right-hand margin is shown the percentage change in inflow. Discussed in text.

This concept, in corollary form, can also be applied to the effect on blood flow of progressively decreasing the caliber of an artery. This has been done in a number of ways. Mann, et al.,[61] found that, in the carotid artery of the dog, a 50 per cent reduction in the lumen could be produced without any change in blood flow, and that a 90 per cent constriction was necessary before a 50 per cent decrease occurred. When graduated, partial compression was applied to the cat's pulmonary

artery,[62, 63] dynamic alterations indicative of significant changes in blood flow appeared only after the diameter had been reduced 52 to 66 per cent. In models, Mann, et al.,[61] found that a 40 per cent reduction in the diameter of the central tube was required to reduce the flow. It should be appreciated that such experiments do not demonstrate the effect of narrowing a vessel upon flow as much as they illustrate how much central constriction is required to make the total resistance significantly greater than the peripheral resistance had been. In the experiments with animal vessels and models, mentioned above, the true effect of narrowing the major artery, i.e., the relation of flow to cross-section area, would have been demonstrated only if there were full peripheral dilatation. This can be illustrated by certain approximations.

In the upper set of diagrams of Fig. 14 a system of tubes represents the arterial tree. A segment 10 units in length represents the central vessel, and a segment 2 units in length represents the peripheral vessels. This is illustrated under three hypothetical circumstances in *A*, *B*, and *C*, in which the segments which represent compositely the small vessels are indicated, respectively, with radii ¼ of, ½ of, and equal to, that of the central vessel. If each unit of length of the central vessel has a resistance of 1, the entire resistance of the central vessel is 10 in each case. The resistance of the peripheral vessel increases as the radius is decreased, and is inversely proportional to some power of the radius between the square and fourth power. For purposes of illustration, the resistance may be considered to vary inversely approximately as the cube of the radius. Therefore, the resistance in the peripheral vessel in *A*, *B*, and *C* of the upper part of Fig. 14 will be 64, 8, and 1, respectively, per unit length. The net resistance of the tubes illustrated will be 138, 26, and 12.

Now let us note the effect of constricting one unit of length of the central vessel to half its diameter in each case, as illustrated in *A*, *B*, and *C* of the lower part of Fig. 14. The central artery resistance is now 1 unit of 8, plus 9 units of 1, or 17, instead of 10, as was the case before. The net effect is to increase the resistances of *A*, *B*, and *C* to 145, 43, and 19 units, respectively. The change in resistance in tubes *A*, *B*, and *C* between the upper and lower parts of Fig. 14 therefore amounts, respectively, to 5 per cent, 30 per cent, and 58 per cent, although the same amount of central constriction had been applied to each in each instance. It is thus apparent that the effect of constriction of a vessel upon the flow through it (with constant inflow pressure) depends not only on the size of that vessel, but also upon the state of the entire system through which the flow occurs.[64] Dilatation of the peripheral vessels makes each central segment relatively more important in its contribution to the total resistance to flow.

The maximum flow may thus be taken to indicate the caliber of the vessels supplying the part, if it appears that, with full dilatation of the peripheral vessels, the diameter of supplying vessel is the limiting

factor in the level of flow attainable. This concept has a certain bearing on disease. Since maximal flow is dependent upon arterial pressure, the "maximum flow" should be greater in hypertension, regardless of cause, unless a certain degree of peripheral resistance, irreversible by whatever dilating method is used, is present as the result of the process leading to hypertension. In peripheral vascular disease, maximal flow studies would indicate reduction of major arterial lumen, as well as the presence of peripheral vessel involvement irreversible by a dilating stimulus. They would not give any indication of distribution of blood flow to various parts of the limb according to needs, for redistribution of flows would not be indicated. Especially is this so because a large part of limb flow is to the skin. Since maximal flow may be thus limited by the caliber of central vessels, the relative merits of peripheral vasodilator procedures cannot be evaluated if these procedures dilate peripheral vessels beyond a point at which the calibers of the more central vessels become appreciable, effective, limiting factors to flow. In this event, their effect can be judged only by the speed and persistence of their action, or by the use of smaller doses. Maximal flow may be conditioned by any effect that the peripheral dilating agent has upon large vessels. Heat may dilate arteries,[23] and the application of occluding cuffs may evoke arterial narrowing.

The importance of recognizing the limitation of flow imposed by a vascular segment applies to all regions of the body in health and disease. It is quite possible that, in some localities, even with full peripheral dilatation, no significant shift occurs in the distribution of effective resistance, and that, in others, even normally, the limiting factor of resting flow is the caliber of the central artery.

SUMMARY AND CONCLUSIONS

The theory and technique of the plethysmographic method of measuring blood flow are critically presented.

When the magnitude of errors which cannot be eliminated is known, much valuable information may be obtained if the limitations of the method are appreciated, and if results are carefully interpreted.

An adequate apparatus for studying the volume of blood flow in the human foot-leg is described.

Values for resting and maximal volume flows on normal subjects are given, and their interpretations discussed. Arterial occlusion as a method of producing dilatation resulting in maximal blood flow was studied.

Evidence is presented to indicate that, under certain circumstances, the caliber of central vessels may be the principal factor which determines the "maximal" volume of blood flow to a region.

Throughout this work the authors received invaluable assistance from Dr. Kenneth Jochim, especially with mechanical and mathematical problems.

The results of our study and those of Wilkins and Eichna (Bull. Johns Hopkins Hosp. **68**: 425, 1941), which were published after the conclusion of this work, are in agreement, especially as regards their extensive observations on reactive hyperemia. Their studies further support the concepts underlying peripheral flow that we have attempted to present.

REFERENCES

1. Stewart, G. N.: Studies on the Circulation in Man. The Blood Flow in the Hands and Feet in Normal and Pathological Cases, Harvey Lectures **8**: 86, 1912.
2. Harris, K. E., and Marvin, H. M.: A Note on the Temperature of Venous Blood and Its Use in Estimating Rate of Blood Flow to the Hand, Heart **14**: 49, 1927.
3. Pickering, G. W.: The Peripheral Resistance in Persistent Arterial Hypertension, Clin. Sc. **2**: 209, 1936.
4. Bierman, W.: Conductive Cooling of Living Human Tissue, Proc. Soc. Exper. Biol. & Med. **42**: 518, 1939.
5. Sheard, C.: Calorimetric Studies of the Extremities. I, J. Clin. Investigation **3**: 327, 1936.
6. Winslow, C.-E. A., Herrington, L. P., and Gagge, A. P.: A New Method of Partitional Calorimetry, Am. J. Physiol. **116**: 641, 1936.
7. Winslow, C.-E. A., Herrington, L. P., and Gagge, A. P.: The Determination of Radiation and Convection Exchanges by Partitional Calorimetry, Am. J. Physiol. **116**: 669, 1936.
8. Burton, A. C.: The Application of the Theory of Heat Flow to the Study of Energy Metabolism, J. Nutrition **7**: 497, 1934.
9. Pickering, G. W.: Observations on the Mechanism of Arterial Hypertension in Acute Nephritis, Clin. Sc. **2**: 363, 1936.
10. Hardy, J. D., and Soderstrom, G. F.: Heat Loss From the Nude Body and Peripheral Blood Flow at Temperatures of 22° C. to 35° C., J. Nutrition **16**: 493, 1938.
11. Hick, F. K., Keeton, R. W., Glickman, N., and Wall, H. C.: Cardiac Output, Peripheral Blood Flow and Blood Volume Changes in Normal Individuals Subjected to Varying Environmental Temperatures, Heating, Piping and Air Conditioning **11**: 50, 1939.
12. Stewart, H. J., and Jack, N. B.: The Effect of Aminophyllin on Peripheral Blood Flow, AM. HEART J. **20**: 205, 1940.
13. Burton, A. C.: The Direct Measurement of Thermal Conductance of the Skin as an Index of Peripheral Blood Flow, Am. J. Physiol. **129**: 326, 1940.
14. Friedlander, M., Silbert, S., and Bierman, W.: Regulation of Circulation in the Skin and Muscles of Lower Extremities, Am. J. M. Sc. **199**: 657, 1940.
15. Lefèvre, J.: Sur la puissance thermogène du foie, et sa participation à la régulation homéotherme chez les sujets non réfrigérés, Compt. rend. Soc. de biol. **77**: 337, 1914.
16. Grant, R. T., and Pearson, R. S. B.: The Blood Circulation in the Human Limb, Clin. Sc. **3**: 119, 1938.
17. Abramson, D. I., Zazeela, H., and Marrus, J.: Plethysmographic Studies of Peripheral Blood Flow in Man. I and II, AM. HEART J. **17**: 194, 206, 1939.
18. Wright, G. M., and Phelps, K.: A Comparison of Procedures for Increasing Blood Flow to the Limbs, Using an Improved Optical Plethysmograph, J. Clin. Investigation **19**: 273, 1940.
19. Brodie, T. G., and Russell, A. E.: On the Determination of the Rate of Blood Flow Through an Organ, J. Physiol. **32**: Proceedings 47, 1905.
20. Hewlett, A. W., and van Zwaluwenburg, J. C.: The Rate of Blood Flow in the Arm, Heart **1**: 87, 1909.
21. Linton, R. R., Morrison, P. J., Ulfelder, H., and Libby, A. L.: Therapeutic Venous Occlusion, AM. HEART J. **21**: 721, 1941.
22. Hamilton, W. F., Woodbury, R. A., and Harper, H. T.: Physiological Relationships Between Intrathoracic, Intraspinal and Arterial Pressures, J. A. M. A. **107**: 853, 1936.
23. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, 1927, Shaw & Sons, Ltd., p. 20.

24. Levy, R. C., and Brams, W. A.: Effect of Arm Compression on Local Venous Pressure in Patients With Normal and Abnormal Hearts, Proc. Soc. Exper. Biol. & Med. **31**: 100, 1933.
25. Burch, G. E., and Sodeman, W. A.: The Estimation of the Subcutaneous Tissue Pressure by a Direct Method, J. Clin. Investigation **16**: 845, 1937.
26. Burton, A. C.: The Range and Variability of the Blood Flow in the Human Fingers and the Vasomotor Regulation of Body Temperature, Am. J. Physiol. **127**: 437, 1939.
27. Prinzmetal, M., and Wilson, C.: The Nature of the Peripheral Resistance in Arterial Hypertension With Special Reference to the Vasomotor System, J. Clin. Investigation **15**: 63, 1936.
28. Wilkins, R. W., Doupe, J., and Newman, H. W.: The Rate of Blood Flow to the Fingers, Clin. Sc. **3**: 403, 1938.
29. Lewis, T., and Grant, R.: Observations Upon Reactive Hyperemia in Man, Heart **12**: 73, 1925.
30. Bock, H. E.: Neuere Untersuchungen über die mechanische Wirkung von Bädern, Ztschr. f. d. ges. phys. Therap. **41**: 42, 1931.
31. Freeman, N. E., and Zeller, J. W.: The Effect of Temperature on the Volume Flow of Blood Through the Sympathectomized Paw of the Dog, Am. J. Physiol. **120**: 475, 1937.
32. Kolin, A.: A New Method of Plethysmometry, Proc. Soc. Exper. Biol. & Med. **42**: 85, 1939.
33. Freeman, N., Shaw, J. L., and Snyder, J. C.: The Peripheral Blood Flow in Surgical Shock, J. Clin. Investigation **15**: 651, 1936.
34. Uprus, V., Gaylor, J. B., and Carmichael, E. A.: Vasodilatation and Vasoconstriction in Response to Cooling the Body. A Criticism of Methods, Clin. Sc. **2**: 301, 1936.
35. Abramson, D. I., Zazeela, H., and Oppenheimer, B. S.: Plethysmographic Studies of Peripheral Blood Flow in Man. III, AM. HEART J. **18**: 290, 1939.
36. Kunkel, P., and Stead, E. A., Jr.: Blood Flow and Vasomotor Reactions in the Foot in Health, in Arteriosclerosis, and in Thromboangiitis Obliterans, J. Clin. Investigation **17**: 715, 1938.
37. Killian, J. A., and Oclassen, C. A.: Comparative Effects of Water Baths and Mustard Baths at Varying Temperatures on the Rate of Peripheral Blood Flow in Man, AM. HEART J. **15**: 425, 1938.
38. Hewlett, A. W.: The Effect of Room Temperature Upon the Blood Flow in the Arm, With a Few Observations on the Effect of Fever, Heart **2**: 230, 1910.
39. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, Am. J. Physiol. **113**: 384, 1935.
40. Bock, A. V., Dill, D. B., and Edwards, H. T.: On the Relation of Changes in Blood Velocity and Volume Flow of Blood to Change of Posture, J. Clin. Investigation **8**: 533, 1930.
41. Nielsen, M., Herrington, L. P., and Winslow, C.-E. A.: The Effect of Posture on the Peripheral Circulation, Am. J. Physiol. **127**: 573, 1939.
42. Lindhard, J.: Effect of Posture on the Output of the Heart, Skandinav. Arch. f. Physiol. **30**: 395, 1913.
43. Field, H., Jr., and Bock, A. V.: Orthopnea and the Effect of Posture Upon the Rate of Blood Flow, J. Clin. Investigation **2**: 67, 1925.
44. Henderson, Y.: Two Lectures on the Efficiency of the Heart and Its Measurement. Lecture 2, Lancet **2**: 1317, 1925.
45. Lawrence, J. S., Hurxthal, L. M., and Bock, A. V.: Variations in Blood Flow With Changes in Position in Normal and Pathologic Subjects, J. Clin. Investigation **3**: 613, 1927.
46. Bock, H. E.: Das Minutenvolumen des Herzens im Liegen und Stehen., Ztschr. f. d. ges. exper. Med. **92**: 782, 1934.
47. Grollman, A.: The Cardiac Output of Man in Health and Disease. Chapter XII. Springfield, Ill., 1932, Charles C Thomas.
48. Goldbloom, A. A., Kramer, M. L., and Lieberson, A.: Clinical Studies in Circulatory Adjustments, Arch. Int. Med. **65**: 178, 1940.
49. Hill, L., and Barnard, H.: The Influence of the Force of Gravity on the Circulation. II, J. Physiol. **21**: 323, 1897.
50. Plesch, J.: Physiology and Pathology of the Heart and Blood Vessels, London, 1937, Oxford University Press, p. 15.

51. Erlanger, J., and Hooker, D. R.: An Experimental Study of Blood Pressure and of Pulse Pressure in Man, Johns Hopkins Hosp. Rep. **12**: 145, 1904.
52. Kendrew, A.: Graphic Registration of Venous Pressure in Man, Heart **13**: 101, 1925.
53. Kunkel, P., Stead, E. A., Jr., and Weiss, S.: Blood Flow and Vasomotor Reactions in the Hand, Forearm, Foot and Calf, J. Clin. Investigation **18**: 225, 1938.
54. Abramson, D. I., Zazeela, H., and Schkoloven, N.: The Vasodilating Action of Various Therapeutic Procedures Which Are Used in the Treatment of Peripheral Vascular Disease, AM. HEART J. **21**: 756, 1941.
55. Grant, R. T., and Bland, E. F.: Observations on Arteriovenous Anastomoses in the Human Skin and in the Bird's Foot, Heart **15**: 385, 1931.
56. Grant, R. T., and Holling, H. E.: Further Observations on the Vascular Responses of the Human Limb to Body Warming, Clin. Sc. **3**: 273, 1938.
57. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, J. Clin. Investigation **11**: 1019, 1932.
58. Dauber, D. V., Landowne, M., Katz, L. N., and Weinberg, H.: Observations on the Interruption and Restoration of the Circulation to the Lower Extremities, J. Clin. Investigation **21**: 19, 1942.
59. Goldblatt, H.: Observations Upon Reactive Hyperemia, Heart **12**: 781, 1925.
60. Stead, E. A., Jr., and Kunkel, P.: Nature of Peripheral Resistance in Arterial Hypertension, J. Clin. Investigation **19**: 25, 1940.
61. Mann, F. C., Herrick, J. F., Essex, H. E., and Baldes, E. J.: The Effect on the Blood Flow of Decreasing the Lumen of a Blood Vessel, Surgery **4**: 249, 1938.
62. Haggart, G. E., and Walker, A. M.: The Physiology of Pulmonary Embolism as Disclosed by Quantitative Occlusion of the Pulmonary Artery, Arch. Surg. **6**: 764, 1923.
63. Gibbon, J. H., Jr., Hopkinson, M., and Churchill, E. D.: Changes in the Circulation Produced by Gradual Occlusion of the Pulmonary Artery, J. Clin. Investigation **11**: 543, 1932.
64. Salzburg, P., and Kubicek, W. G.: A New Method for Regulated Vascular Obstruction, Proc. Soc. Exper. Biol. & Med. **45**: 831, 1940.

THE INTERNAL PNEUMOCARDIOGRAM*

ALDO LUISADA, M.D.
BOSTON, MASS.

Definition.—The term "pneumocardiogram" is here applied to the tracing of the pressure changes which occur in the air passages of the lungs as a consequence of the heart beat.

Previous terms for the same phenomenon include the following: "negative thoracic pulse," "cardiopneumatic waves," "respiratory pulse," "heart notchings," and "heart interruptions of the respiratory curve."

History.—Old physiologic studies showed that the heart beat is accompanied by changes of pressure within the thorax. The heart beat causes a movement of air through the upper respiratory passages which, under normal conditions, is not accompanied by any perceptible sound. In the presence of disease, however, the air movement through the nostrils and mouth may be affected by the heart in such a way that the observer becomes aware of it, and there may even be a subjective sensation, which may account for many early studies on patients.

Clinical Studies.—The first clinical observations were made between 1867 and 1888 by Friedreich,[1] Galvagni,[2, 3] and Cheesmann,[4] who were followed, in later years, by Gerini,[5] Fischer,[6] Binetti,[7] and Lang.[8] Evident tracheal or oral murmurs with a cardiac rhythm were described by these authors in many diseases, especially in connection with aortic insufficiency and aortic aneurysm. The important contributions of Galvagni on "oral auscultation" should be mentioned, and also the name "oral whiff," coined by Cheesmann.

Graphic Studies.—In 1861, Buisson[9] described, after animal experimentation, the so-called "negative thoracic pulse" caused by the decrease in the volume of the heart as a result of ventricular systole. Bert[10] studied from the trachea the rhythmic oscillations due to the movements of the heart. Landois,[11] in 1876, obtained records of air pulsations from the mouths of normal people. He described *negative waves* which occurred when the glottis was open (cardiopneumatic waves), and *positive waves* when the glottis was closed. The latter were

From the Middlesex University Medical School.
Received for publication June 13, 1941.

*The term "pneumocardiogram" has been recently employed by H. A. Blair and A. M. Wedd (AM. HEART J. 17: 536, 1939). They make use of this term with reference to the rapid changes of chest volume caused by the heart beat. Their records and mine register essentially the same phenomena. However, inasmuch as the techniques were not the same, and the results are probably also different, it would avoid confusion to call my records "internal pneumocardiograms." This implies that there is a direct connection between the recorded waves and the intrapulmonary pressure. The records of Blair and Wedd should be called "external pneumocardiograms."

due to the pulsation of the buccopharyngeal vessels when the mouth and pharynx became a closed cavity as a result of closure of the glottis.

Two years later, Mosso[13] studied, by means of Marey tambours, cardiopneumatic tracings on man, and described a *double-notched systolic wave* due to a systolic diminution of the pressure in the thorax. He attributed the first notch to dilatation of the thorax caused by the apex beat, and the second to the diminution of heart volume. However, his records, which were reproduced by Luciani in his textbook,[14] do not confirm this explanation.

The successive researches of Klemensiewicz[15] and of Haykraft and Edie[16] led to the conclusion that the chief part of the pulsations was due to rhythmic compression of the lung by the heart apex. This conclusion seemed to be supported by the fact that opening the thorax did not abolish the pulsations. François-Frank,[17] however, attributed the persisting waves to the pulsation of the pulmonary vessels, which could not be recorded when the thorax was closed.

The technique of making graphic records from the nose was later applied to patients by Siciliano,[18] Cremer and Matthes,[19] and Frugoni.[20] In their cases only a single negative wave was described, but it had quite a marked intensity.

In 1918, Klewitz[21] gave a description of many more details of the cardiac waves of the respiratory curve. He described a small negative wave during auricular systole, and a large negative wave during ventricular systole. Between the two a small positive notch was present, and another was found at the time of closure of the aortic valves.

Pneumotachographic Studies.—A third phase started with the description of the pneumotachograph, an apparatus which enables one to study the velocity of air flow during normal respiration. Fleisch[22] and his co-worker, Bretschger,[23] gave all details of physiologic pneumotachograms.

In 1928 I observed a group of normal people and cardiac patients and studied the heart waves of the respiratory curve, employing the Fleisch pneumotachograph, as well as the older technique, modified by the use of a Frank capsule.[24]

These studies demonstrated that the waves caused by the heart beat are quite similar in both records. They are quicker in the pneumotachogram, and slower, but often more evident, in the pressure records. A real retrogression of the air stream takes place only when systole occurs in the phase between inspiration and expiration. Otherwise, the waves due to the heart beat cause only a diminution of speed.

At that time I described three chief negative waves: (1) a presystolic wave coinciding with auricular systole (''*a*'' wave), (2) a systolic wave coinciding with ventricular systole (''*v*'' wave), and (3) a diastolic wave following the closure of the aortic valves (''*d*'' wave).

The possibility of positive waves between the negative depressions was not excluded. A marked increase of the auricular *a* wave in mitral

valve defects and of the ventricular *v* wave in aortic insufficiency and hypertensive patients were the chief results of my clinical studies.

The necessity of avoiding closure of the glottis was confirmed by the high positive pulse which sometimes occurred in less trained patients if they were asked to hold their breath.

A year later, Hochrein and Weiss[25] studied, by means of the Hochrein pneumotachograph, the pulsations of the air column which are caused by the heart beat. They found small notches on the respiratory curve, but studied them only during inspiratory or expiratory standstill. No definite notchings were observed by them in normal people during respiratory standstill. Notchlike elevations were found in both inspiratory and expiratory standstill in patients with aortic aneurysm, but only during the inspiratory standstill in patients with adhesive pericarditis. The study was extended later by Hochrein[26] and by Hochrein and Laplace[27] on patients with adhesive pericarditis and on experimental animals. The technique of these studies and their results were discussed by Fleisch,[28] Holzlöhner,[29] Hitzenberger and Hinteregger,[30] and Luisada.[31]

In 1935 and 1936, some new physiologic and clinical studies were published by me[31-33] and by my co-worker, Rubino.[34] Rubino recorded simultaneously the intrathoracic pressure on the right side and the nasal tracing and found an absolute similarity of details. This eliminated any possibility that the apex beat is a causative factor.

Among the chief clinical results of these studies should be mentioned (a) the tremendous increase in size of the systolic *v* wave in aortic insufficiency,[32, 34] (b) the increase of all waves, but chiefly of the auricular *a* wave, in patients with mitral disease,[32, 34] and (c) the gigantic negative wave, followed immediately by a positive one, which occurs during systole in patients with tricuspid insufficiency.[31, 32]

Later Studies.—The most recent studies were carried out on normal people by Holzlöhner.[35, 36] This author studied the records obtained by the pneumotachograph and the dielectrograph, and pressure curves from the mouth. By using the pneumotachograph with a string anemometer, he obtained much clearer details of the curve. In the recumbent position the chief deflection is a downward early systolic wave, which is followed by a small upright and a second small downward systolic wave. A small presystolic and a small diastolic wave are also present. Marked modifications, either following changes in position, or due to the difference between expiratory and inspiratory standstill, were also described by him. He explains all the recorded waves by the difference between inflow to, and outflow from, the thorax, and excludes any change caused by either the apex beat or diaphragmatic pulsations.

The changes due to position and to respiratory phase were explained by the unlike action of the systolic aspiration on the large veins, in

which a different tension occurs. The changes dependent upon position should be known in order to be able to use a uniform technique.

Comparative studies of different methods showed Holzlöhner that the pressure curves were more like air velocity tracings than volume curves, but had something in common with both. No fundamental difference was found between pressure and air velocity curves, and all the typical points of inversion of the waves were found to be identical.

TECHNIQUE

I have endeavored to find a new and easy technique which could reproduce all details of the pneumocardiogram and enable the physician to use this kind of tracings routinely. I have avoided, therefore, every technical device (pneumotachograph, mask), and everything else (special position, mouth tube, respiratory standstill) which requires special training of either the physician or the patient.

Apparatus.—I have used a Sanborn Stetho-Cardiette[37] for the simultaneous registration of the pneumocardiogram and the heart sounds. A comparison of the pneumocardiogram with the phonocardiogram permits an analysis of the component waves of the former. A Sanborn piezoelectric microphone, such as is usually employed for sphygmographic purposes,[37, 38] was also used. To this I added a high-pass filter for decreasing the intensity of the slow respiratory deflections without curtailing the quick pulsations caused by the heart beat. The plug of the sphygmographic microphone is inserted into the filter, and the plug of the filter is inserted into the electrocardiograph. A control arrangement on the filter is used for varying the degree of attenuation upon the slow respiratory deflections. Some experiments were performed in which three simultaneous registrations were employed. The apparatus for this purpose was the Sanborn Tri-Beam Stetho-Cardiette.[37]

Tracing and Standardization.—A rubber tube, 10 inches long, is connected to the microphone. It ends in a bakelite olive which is inserted into one of the nostrils of the patient. The patient is placed in a comfortable sitting position, with complete muscular relaxation. A semirecumbent position may also be employed. The physician must instruct the patient to breath normally through the nose (with the mouth closed).

With the above-described arrangement, the pneumocardiogram is registered in a manner similar to that for an electrocardiographic lead. During the normal breathing of the patient two operating adjustments may be made: (1) the degree of filter attenuation upon slow respiratory waves, and (2) the registration sensitivity of the electrocardiograph. By regulating both, the physician can obtain a tracing in which the waves will be from 1 to 2 cm. high, and even the extreme phases of respiration will be recorded within the limits of the sensitized paper. The pneumocardiogram is normally registered at a paper speed of 75 mm. per second.

A mechanism* was employed for the standardization of the pneumocardiographic deflections. This is merely a device which produces a known change of pressure in the pneumocardiographic tube which is connected to the patient's nostril. The pneumocardiographic deflections may then be expressed in millimeters of water if none of the conditions of the experiment were changed.

The above-described technique has the following advantageous characteristics: (a) possibility of accomplishing the work with a commercially obtainable apparatus,

*Supplied by the Sanborn Co.

(b) no special training required on the part of the patient, and (c) correct registration of every slight change of pressure of the air caused by the heart beat.*

DESCRIPTION AND EXPLANATION OF THE RECORDS

The average pneumocardiogram possesses a typical characteristic which will now be described. It has, fundamentally, five negative

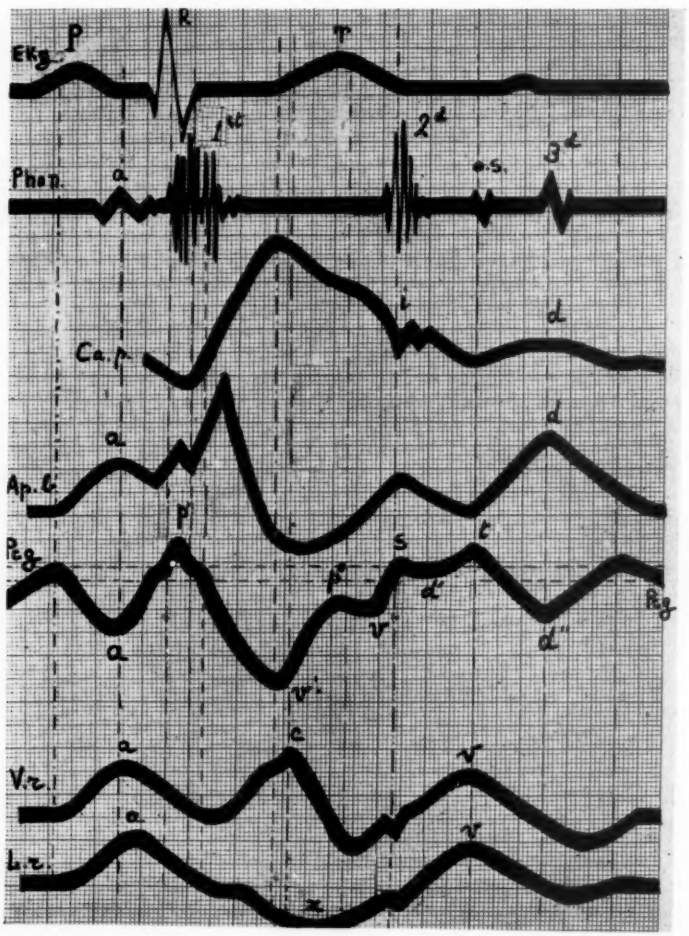


Fig. 1.—Schematic drawing of the pneumocardiogram and time relation of its waves with the waves of the different tracings. *Ekg,* electrocardiogram; *Phon.,* phonocardiogram; *Ca.p.,* carotid pulse; *Ap.b.,* apex beat; *Pcg.,* pneumocardiogram; *V.r.,* venous record on the jugular vein; *L.r.,* liver record.

waves, each with a definite connection with the phases of the cardiac action. Positive waves are also present, and bear a definite relation-

*The electrical filter circuit which has been previously described does not remove every trace of the low-frequency components caused by respiration. Thus, some waves may be seen in a pneumocardiogram in one cycle and not in a succeeding one, because of the unlike rhythm of respiration and cardiac action. These respiratory components are more marked in children and excitable adults. Pneumocardiographic waves may be differentiated from respiratory waves because they occur in every succeeding cardiac cycle, although they may be somewhat modified in contour.

TABLE I

NAME OF WAVE	DIRECTION	PHASE	COINCIDENCE				
			EKG	HEART SOUNDS	CAROTID PULSE	JUGULAR RECORD	APEX TRACING
a (Auricular)	Downward	Presystolic	Between P and Q	Auricular vibrations		*a* wave	*a* wave
p^1 (Papillary muscles contraction)	Upright	Closure of tricuspid valve; starts ventricular systole	With R-S	First part of first sound	Before rising of tracing	Before bottom of wave between *a* and *c*	Slightly before notch of semilunar valves opening
v^1 (First ventricular wave)	Downward	Early systolic	Between S and T	End of first sound and after it	With first part of carotid pulse	With *c* wave	With first part of tracing (upright then downward wave)
p^2 (Peripheral pulse)	Upright	Midsystolic	Beginning of T	Between first and second sounds	Immediately after apex of pulse wave	Descending phase of *c*	Bottom of systolic depression
v^2 (Second ventricular wave)	Downward	Late systolic	During T	Before second sound	Before incisura	Bottom between *c* and *v*	
s (Semilunar valve closure)	Upright	Closure of aortic valves; ends ventricular systole	End of T	Second sound	Incisura	Notch recording second sound	Peak of wave recording closure of semilunar valves
d^1 (First diastolic wave)	Downward	Interval between semilunar valve closure and A-V valves opening	After T	After second sound	During oscillations following incisura	Ascending part of *v*	Descending part of tracing
t (Tricuspid valve opening)	Upright	Opening of tricuspid valve		Eventual opening snap of mitral valve		Apex of *v* wave	Bottom of depression
d^2 (Second diastolic wave)	Downward	Rapid filling of ventricles		Third sound	Dicrotic wave	Descending part of *v*	Peak of wave marking rapid filling

ship to cardiac action. Essentially, there are only two positive waves. Positive waves are those which reach a level above the base line (Fig. 1). The junction point between some of the adjacent negative waves may become more positive and reach an amplitude above the base line.

The following description and Table I should be compared with Fig. 1, which represents the average of our normal records. Actual pneumocardiograms are reproduced in the following figures.

In describing the component waves, I have not altered the nomenclature used in 1928. There is a larger number of waves because of better recordings, so that the *v* wave and the *d* wave are now split in two, and bear the names v^1 and v^2, d^1 and d^2. The initials *a*, *v*, *d*, etc., are the first letters of the terms they represent and are, therefore, easy to remember.

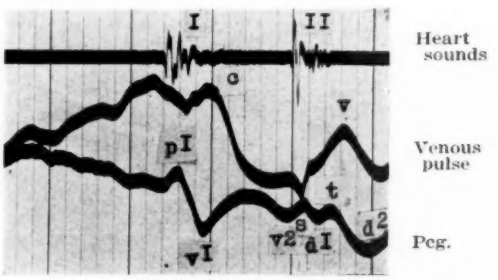


Fig. 2.—Heart sounds, pneumocardiogram, and jugular record in recumbent position. Simultaneous occurrence of the notches and of the second sound. *v* occurs at the same time as the *v* wave of the jugular record. The wave d^2 slightly precedes the bottom of the depression following the *v* wave of the jugular record.

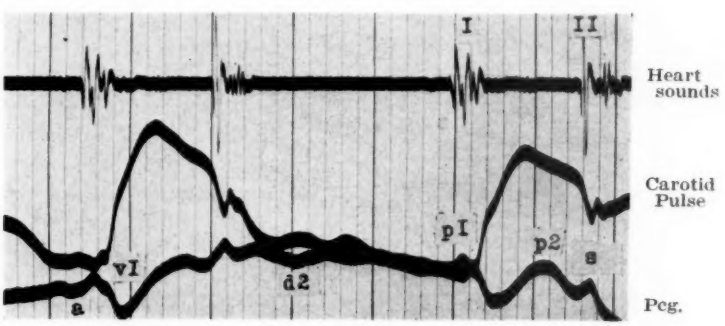


Fig. 3.—Heart sounds, carotid pulse, and pneumocardiogram in recumbent position. Time relation of *p.v*, p^2, and v^2 with the chief wave of the carotid pulse.

During presystole, the phase in which the auricles contract, there is a negative wave in the pneumocardiogram. It is designated as the *a* wave, or auricular wave. It is produced by stasis of blood, and often by backflow in the large veins, caused by the contraction of the right auricle. Arterial outflow plus venous stasis (or slight venous outflow) cause an inrush of air into the thorax, and therefore a depression in the pneumocardiogram (Figs. 3, 8).

Beginning of Systole.—Before the jugular pulsation reaches the bottom between *a* and *c* (see Figs. 1, 2), a small positive wave occurs in the pneumocardiogram. The systolic wave of the apex beat at this phase of the cycle is just beginning, and the carotid pulsation has not yet commenced (Figs. 2, 3).

A tentative explanation is as follows: At the beginning of ventricular systole the auriculoventricular valves are slightly raised in order to close the openings, then are lowered by the contraction of the papillary muscles. This movement creates a slight aspiration of blood into the right auricle, with a resulting small outflow of air from the thorax.

This notch will be called p^1 (*contraction of the papillary muscles,* or *first positive wave,* Figs. 2, 3, 8).

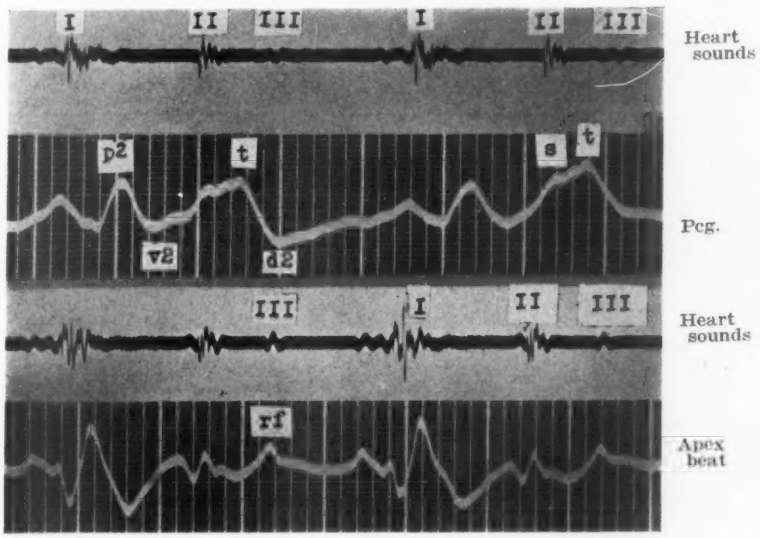


Fig. 4.—*A,* Record of a normal person in recumbent position. Heart sounds and pneumocardiogram. Third heart sound occurs at the same time as d^2. *B,* Record of the same person. Heart sounds and apex beat. The third sound is caused by rapid filling of the ventricles.

Previously, I attributed this small notch to the pulsation of the pulmonary vessels, but this explanation has been shown to be incorrect by experimental researches on dogs. When large openings are made in the dog thorax, the waves due to the movements of the heart disappear. Only small vibrations caused by the close contact of the heart and the mediastinal lobe are present. However, a new positive wave appears during the *second half* of systole which is due to the pulsation of the pulmonary vessels (Fig. 5).

First Half of Systole.—The blood leaves the thorax through the branches of the aortic arch and the abdominal aorta. At the same time, the venous blood either moves slowly toward the right auricle (lower vena cava, as seen in liver tracings), or has a short backflow (upper

vena cava—*c* wave of the jugular vein tracings). In this phase there is considerable aspiration of the air into the thorax, with a resulting depression in the pneumocardiogram. This wave, which is often the most marked of all, will be called v^1 (*first ventricular wave*, Figs. 2, 3, 4, 6, 8).

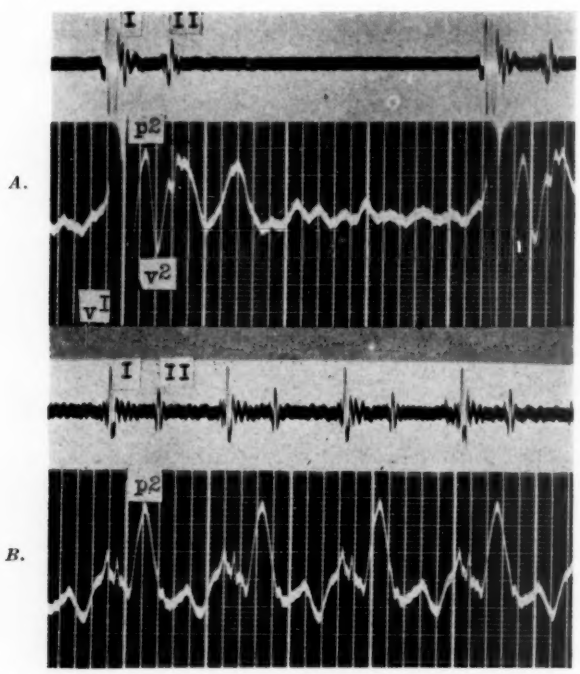


Fig. 5.—Heart sounds and pneumocardiogram of a dog under anesthesia. *A*, With closed thorax. *B*, With open thorax. The chief downward deflection is replaced by small vibrations. The systolic wave p^2 is present (pulsation of the pulmonary vessels). The diastolic waves are absent when the thorax is opened.

Midsystole.—After the first part of systole a series of changes occurs in the dynamics of the thorax. Pronounced aspiration is exerted on the veins by the increased negative pressure within the thorax and by a lowering of the floor of the right auricle. This causes a quick flow of venous blood into the right auricle from both venae cavae, as shown by the jugular and the liver tracings. In some cases this onrushing flow may be greater than the outflowing arterial blood. Therefore, the pneumocardiogram will show an upright notch which normally does not reach the zero line, but in some cases may have a positive value.

The pulsation of the pulmonary arteries (Fig. 7)* and that of the tracheal and nasopharyngeal vessels also contribute to the formation of

*Theoretically, the pulsation of the pulmonary vessels should not produce any change on the pneumocardiogram, because the blood movement is intrathoracic. However, the contact between small lung arteries and alveolar air is so intimate that the following occurrence is quite probable: The decreased volume of the right ventricle will affect the venous flow to a greater extent, and the increased volume of the lungs will have greater effect on the air flow.

this wave. The name of this wave will be p^2 (*peripheral pulse*, or *second positive wave*, Figs. 2, 4, 6, 8).

Second Half of Systole.—In this phase little blood enters the thorax, as the right auricle is nearly filled. At the same time the blood continues its outflow from the aortic arch into the peripheral vessels. Therefore, a negative wave occurs in the pneumocardiogram, as evidence of the inflow of air into the thorax. In some cases this wave is larger than v^1 (see Figs. 2 and 4*A*). The name of this wave will be v^2 (*second ventricular wave*).

Closure of Aortic and Pulmonary Valves.—The former phase ends abruptly with the closure of the aortic valve, which is evidenced by the presence of the aortic second sound. An upright notch occurs in the pneumocardiogram simultaneously with the second sound and with the incisura of the carotid pulse. We shall designate this wave of the pneumocardiogram by the letter *s* (*semilunar valve closure*, Figs. 2 and 3).

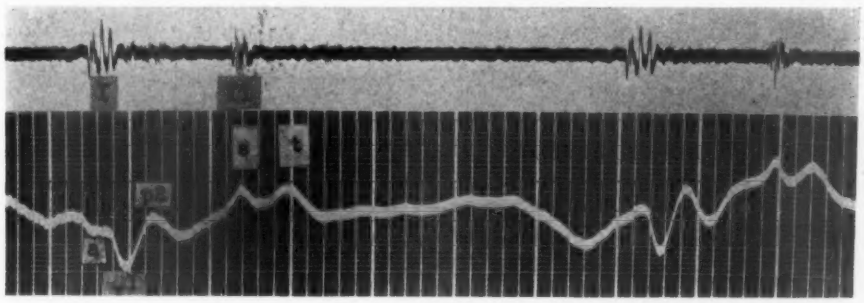


Fig. 6.—Heart sounds and pneumocardiogram in a patient with bradycardia (43 per minute).

First Part of Diastole.—A short time elapses between the closure of the aortic valve and the opening of the tricuspid valve. During this phase either a small downward wave or a straight line is seen in the pneumocardiogram. This wave we shall call d^1 (*first diastolic wave*, see Figs. 1, 2, 8*C*).

Opening of the Tricuspid Valve.—The opening of the tricuspid valve causes a sudden onrush of blood from the venoauricular reservoir into the right ventricle. The moment of transition is indicated by a fairly clear upright notch, which may become a decidedly positive wave. Its designation will be *t* wave (*tricuspid valve opening*). It occurs simultaneously with the lowest point of the apex record, and with, or before, the peak of the venous pulse *v* wave (Figs. 1, 2, 4).

Second Part of Diastole.—An increased amount of blood leaves the thorax at the time of the dicrotic wave in the aorta. During this phase the aortic valve is closed, but the elastic retraction of the aorta still forces blood into the periphery. Blood rushes quickly from the right auricle into the right ventricle because of the difference in pressure.

Because of a tonic adaptation of the right auricle, the amount of venous blood which enters the auricle at this time is not very large. There occurs, as a result, an inflow of air into the thorax which causes a deep negative wave in the pneumocardiogram (d^2, or second diastolic wave). It is important to mention at this time that the peak of the diastolic wave of the apex cardiogram occurs simultaneously with d^2 of the pneumocardiogram. The *third heart sound*, which indicates rapid filling of the ventricles, occurs simultaneously with the point of maximum depression of d^2 (Fig. 4).

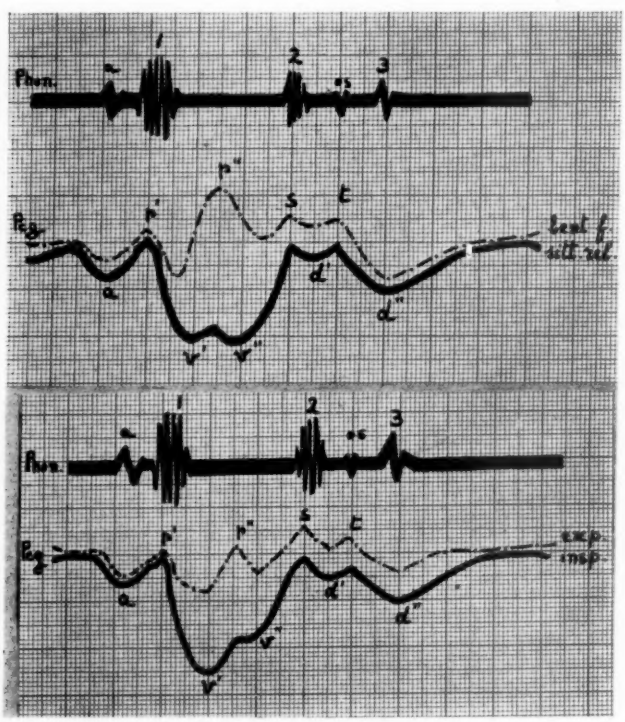


Fig. 7.—Schematic drawing of the changes due to respiration and position. *A.* ————, sitting relaxed; -.-.-.-.-., bent forward. *B.* ————, inspiration; -.-.-.-.-, expiration.

A number of additional diastolic waves may occur in the pneumocardiogram when diastole is prolonged; they are the result of changes of pressure in the thorax. Additional negative waves in the pneumocardiogram may be called d^3, d^4, etc. (*late diastolic waves*).

PHYSIOLOGIC VARIATIONS IN THE PNEUMOCARDIOGRAM

Respiratory Changes.—By placing the hand on the abdomen of the patient, and indicating each abdominal depression on the record with the lead marker during each expiration, it is possible to distinguish between the two phases of respiration. During the first portion of

inspiration, normal persons show deeper waves in the pneumocardiogram than during other phases. However, the clarity of the record is at times not perfect during this phase, and two waves may combine as a single wave. The *a* wave is deep and broad; p^2 is smaller and of a short duration. V^1 and v^2 show a tendency to form a single, negative, systolic wave (Fig. 7).

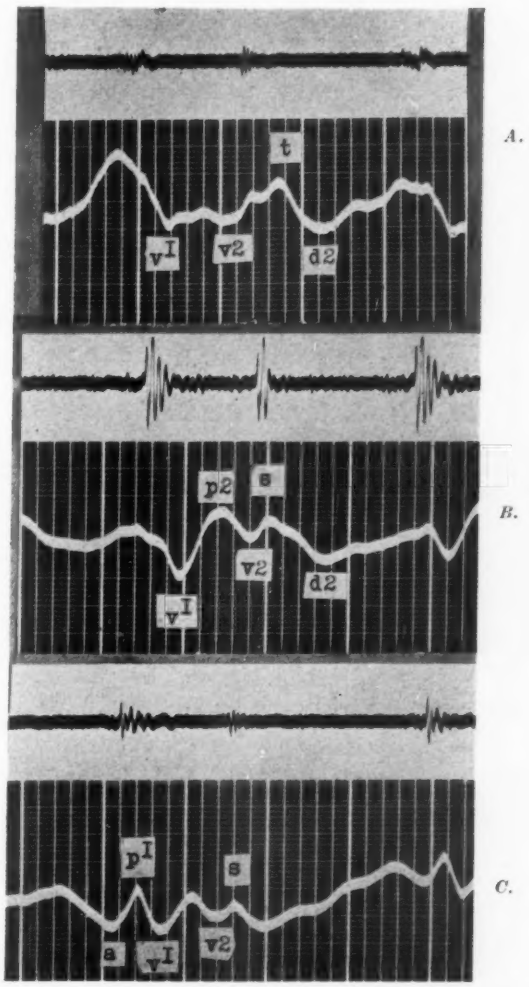


Fig. 8.—Changes in heart sounds and pneumocardiogram in different positions (normal person). Same phase of respiration. *A*, recumbent; *B*, sitting bent forward; *C*, standing.

During *expiration* normal persons usually show smaller waves. This is particularly true in the second half of the phase. P^1 is usually clearly defined and sharp, and p^2 is tall and broad, with a definite positivity. *T* possesses a low amplitude, but *s* is taller and often well defined (Fig. 7*B*).

Inspiratory and Expiratory Standstill.—The above described technique eliminates the necessity of requesting the patient to hold his breath in an extreme inspiratory or expiratory position, which may introduce individual variations and abnormal pressure conditions. A study was made of these extreme phases in order to compare the new technique with that used by previous observers. From a practical standpoint it has been found that the degree of inspiration or expiration is a variable quantity which depends upon the training and cooperation of the patient. There was no fundamental difference in timing or in the polarity of the waves between the changes produced in the pneumocardiogram by normal physiologic respiratory phases and those resulting from an artificial pause in the extreme positions of the thorax.

Changes Due to Position.—The best results are obtained in either a sitting position or a semirecumbent position, with the patient completely relaxed. Other positions, such as supine, sitting erect, sitting bent forward, or standing, may produce many important changes in the pneumocardiogram. Many of these changes were studied by Holzlöhner, and were explained by him as the result of an altered venous flow caused by modified tension of the venous wall. Figs. 7 and 8 indicate some of the changes brought about by different positions. In general, the difference between the sitting and semirecumbent positions is unimportant. Relaxation of all muscles is necessary in order to avoid error.

Bradycardia and Tachycardia.—Because of the shortness of diastole, persons with tachycardia often show a partial or total fusion of d^2 and a. The amplitude of the wave between s and t is often increased.

These variations may be explained by similar changes in diastolic venous inflow and by the abrupt systolic collapse of the veins.

In bradycardia, on the other hand, the waves are typical, and a number of additional waves, such as d^3 and d^4, may occur during diastole.

THE PRACTICAL VALUE OF THE PNEUMOCARDIOGRAM

The pneumocardiogram has a number of important clinical applications. Routine clinical phonocardiography has indicated to me that at times it is rather difficult to explain the nature of one or more extra sounds which may occur in the cardiac cycle. The phlebogram is at times unreliable for this purpose. For instance, the use of the venous pulse v wave for the differentiation between an *opening snap* of the mitral valve and the *third sound* is sometimes erroneous. This has been observed by Taquini, Walsh, and Massell[39] in cases of mitral regurgitation, in which the isometric relaxation phase may be shortened. The result is that the *third heart sound* occurs approximately where the *opening snap* should be. I have observed a number of normal persons whose *third sound* almost coincided with the peak of the v wave.

The apex cardiogram, as indicated by Taquini, et al., is more reliable. However, the apex cardiogram is not always recordable. The pneumocardiogram, for this differentiation, is always recordable with the new technique. In taking a large number of pneumocardiograms with this new technique, I have observed that there is a constant time relationship between four waves of the pneumocardiogram and four phases of the heart cycle, namely:

p^1 = closure of the tricuspid valve
s = closure of the aortic valve
t = opening of the tricuspid valve
d^2 = rapid inflow into the ventricles

Three of these pneumocardiographic waves coincide with definite acoustic phenomena which are, or may be, present in normal persons and/or in pathologic conditions, namely:

s = second heart sound
t = "opening snap" of the mitral valve
d^2 = third heart sound

The relationship between pneumocardiographic and phonocardiographic waves is constant, although the contour of these waves may vary from person to person. Future experience should indicate whether the pneumocardiogram will also have diagnostic value with respect to asynchronous valve closure of the two ventricles.

Study of the pneumocardiogram in valvular defects and in arrhythmias has been carried out on a fairly large scale by previous authors and by me. However, in my opinion, the development of superior apparatus which allows the employment of this new pneumocardiographic technique warrants a repetition of the study in order to establish a more exact basis for the variations brought about by various cardiac abnormalities. It is conceivable that some of the typical changes that occur in the pneumocardiogram may assume a diagnostic value.

SUMMARY

1. There are rhythmic pulsations in the respiratory air passages which are caused by the heart beat.

2. A new and easily applied technique is described for the graphic registration of the cardiac waves during every phase of normal respiration. I suggest calling this tracing the internal *pneumocardiogram*, a name which is self-explanatory.

3. Pneumocardiograms were obtained on normal persons, and the component waves are herein analyzed.

4. As a result of previous and recent experiments (intrathoracic pressure records in man, opening of the thorax in animals), the possibility that the apex beat causes these waves is eliminated.

5. Multiple waves are produced in the pneumocardiogram by the difference between venous inflow to, and arterial outflow from, the thorax.

6. Five negative and four positive waves are described.

7. The coincidence between three of the positive waves and valvular movements is demonstrated. The coincidence of one of the negative waves with rapid filling of the ventricles is also established.

8. Changes brought about by different positions and by respiratory phases have been studied.

9. The importance of the pneumocardiogram in clinical diagnosis has been indicated.

REFERENCES

1. Friedreich: Herzkrankheiten, Berlin, 1875.
2. Galvagni, E.: Ueber die Auskultation der Mundhöhle, Mediz. Jahrbücher, Hefte 2, 1875.
3. Galvagni, E.: Sopra uno speciale fenomeno appartenente alla ascoltazione della bocca, Clin. med. ital. 436, 1904.
4. Cheesmann: The Oral Whiff, New York Herald, March 3, 1888.
5. Gerini, C.: Sui rumori cardio-vascolo-polmonari, Riv. crit. clin. med. 13, 1901.
6. Fischer: Das Mundhohlgeräusch, München. med. Wchnschr. 821, 1903.
7. Binetti: Sull 'ascoltazione della bocca, Gazz. d. osp. 133, 1905.
8. Lang: Ueber einige durch die Herzaktion verursachten Bewegungen der Brustwand, Deutsches Arch. f. klin. Med. **108**: 35, 1912.
9. Buisson: Quoted by Luciani.
10. Bert, P.: Quoted by Luciani.
11. Landois: Traité de Physiologie.
12. Luciani, L.: Delle oscillazioni della pressione intratoracica e intraddominale, Arch. di Bizz., 2, 1877.
13. Mosso, A.: Sul polso toracico negativo, Arch. di Bizz., 2, 1878.
14. Luciani, L.: Fisiológia dell'uomo, Milano, S. E. L., 1923.
15. Klemensiewicz: Quoted by Klewitz.
16. Haykraft, J. B., and R. Edie: Cardio-Pneumatic Movements, J. Phys. **12**: 426, 1891.
17. François-Frank: Quoted by Klewitz.
18. Siciliano, L.: Su alcune particolarità del tracciato cardio-pneumatico, Clin. med. ital. N. 9, 1903.
19. Cremer and Matthes: Quoted by Klewitz.
20. Frugoni, C.: Espirazione cardio-sistolicamente intercisa e polso toracico negativo, Riv. crit. clin. med. **15**: 100, 1914.
21. Klewitz, F.: Die kardiopneumatische Kurve, Deutsches Arch. f. klin. Med. **124**: 460, 1918.
22. Fleisch, A.: Das Pneumotachogramm, Pflüger's Arch. f. d. ges. Physiol. **209**: 713, 1925.
23. Bretschger: Das normale Pneumotachogramm, Arch. f. d. ges. Physiol. **210**: 134, 1925.
24. Luisada, A.: Le intercisioni del respiro di origine circolatoria, Minerva Med. **8**: 1139, 1928.
25. Hochrein, M., and Weiss, S.: The Pneumotachogram in Certain Intrathoracic Diseases, Arch. Int. Med. **44**: 289, 1929.
26. Hochrein, M.: Ueber die herzsychronen Zacken im Pneumotachogramm, Med. Klin. 1203, 1932.
27. Hochrein, M., and Laplace, L.: Der pneumotachographische Nachweis der Pericarditis Adhaesiva, Deutsches Arch. f. klin. Med. **176**: 113, 1933.
28. Fleisch, A.: Vergleichende Untersuchungen ueber Pneumotachographen, Pflüger's Arch. f. d. ges. Physiol. **227**: 322, 1931.
29. Holzlöhner, E.: Die Volumenänderungen im menschlichen Thorax während der Herzaktion, Ztschr. f. Biol. **92**: 293, 1932.
30. Hitzenberger, K., and Hinteregger, F.: Ueber die herzsynchronen Zacken im Pneumotachogramm, Med. Klin. **28**: 972, 1932, and **28**: 1204, 1932.
31. Luisada, A.: Le Mediastino—Pericarditi Adesive—Report to the 41st Meeting of Ital. Soc. Int. Med. (Rome, 1935).

32. Luisada, A.: Ueber die Bedeutung der Respirationskurve bei den verschiedenen Erkrankungen des Herzens, Verhandl. d. deutsch. Gesellsch. f. inn. Med., 8 Tagung, 1935.
33. Luisada, A.: Singolare associazione di vizio combinato di cuore con fegato candito, Arch. di pat. e clin. med. **16**: 404, 1936.
34. Rubino, A.: I fenomeni pulsatori del respiro nei soggetti normali e nelle malattie cardio-vasali, Folia med. **22**: 435, 1936.
35. Holzlöhner, E.: Der Atempuls und der Blutrückstrom zum Herzen, Ztschr. Biol. **97**: 409, 1936, and **98**: 281, 1937.
36. Holzlöhner, E.: Der Atempuls des Menschen und der Blutstrom in den herznahen Venen, Arch. f. Kreislaufforsch. **1**: 305, 1937.
37. Rappaport, M. B., and Sprague, H. B.: Physiologic and Physical Laws That Govern Auscultation, and Their Clinical Application, AM. HEART J. **21**: 257, 1941.
38. Miller, A., and White, P. D.: Crystal Microphone for Pulse Wave Recording, AM. HEART J. **21**: 504, 1941.
39. Taquini, A., Walsh, B. J., and Massell, B. F.: Phonocardiographic Studies of Early Rheumatic Mitral Disease, AM. HEART J. **20**: 295, 1940.

ELECTROCARDIOGRAPHIC CHANGES IN BRONCHIAL ASTHMA AND THEIR SIGNIFICANCE

JOSEPH HARKAVY, M.D., AND ALFRED ROMANOFF, M.D.
NEW YORK, N. Y.

IN A recent communication by one of us (J. H.),[1] clinical and pathologic evidence was presented in support of the concept that the electrocardiographic abnormalities associated with asthmatic attacks in certain cases of bronchial asthma were manifestations of an underlying hyperergic vascular disease. This work suggested study, with special reference to the electrocardiograms, of an additional group of fifty patients with bronchial asthma who were admitted to the hospital during the past five years. Persons with evidence of organic heart disease, hypertension, generalized arteriosclerosis, or other associated illnesses were excluded from this investigation.

Although electrocardiographic abnormalities in bronchial asthma have been described by various authors, no attempt has been made to interpret the mechanism involved in their evolution. Kahn[2] called attention to the frequency of right axis deviation, and noted the presence of enlarged P waves in four of ten cases in which there was right axis deviation. Unger,[3] in reviewing seventy-four cases, also found right axis deviation which was well developed in four cases and suggestive in thirty-five. Criep,[4] in a study of eight patients during acute paroxysms of asthma, observed that six had normal electrocardiograms, one had abnormalities of conduction, characterized by an increase in the P-R interval, and another had extrasystoles. Colton and Ziskin[5] reported delayed conduction, arborization block, and negative T waves in eleven, or 20 per cent, of fifty cases of bronchial asthma. They regarded these changes as evidence of myocardial involvement which appeared only in those patients who had had asthma ten years or longer. In one case they observed T-wave inversion which disappeared with the subsidence of the paroxysmal attacks.

Of the fifty patients investigated in this study, twenty presented the following electrocardiographic changes, exclusive of sinus tachycardia: (1) prominent P waves, (2) QRS disturbances, (3) RS-T transition changes, and (4) T-wave alterations (Table I).

From the Medical Department of the Mount Sinai Hospital, New York, N. Y.
Read before the American Society for the Study of Allergy, June 10, 1940.
Received for publication Nov. 10, 1941.

SUMMARY OF THE CLINICAL OBSERVATIONS

A review of the constitutional background of the twenty patients indicated the presence of a personal or family history of allergy in only five. Sinus infection proved to be the major exciting agent in eighteen of the cases, and, in eight of these, food and inhalant sensitivity, including pollen, was likewise demonstrable. The provocative factors in the remaining two cases were not ascertained. The duration of the asthma varied from eight months to thirty-four years. The youngest patient in the series was 18, and the oldest, 60 years of age (Table I).

Pulmonary Lesions.—Examination of the lungs disclosed the sonorous râles which are characteristic of bronchial asthma in all of the twenty cases. In the majority of the cases, in spite of the dyspnea, there was no severe cyanosis. Roentgenologic examination of the lungs during acute paroxysms revealed pulmonary infiltration in six cases (Cases 1, 8, 9, 13, 14, and 16). These lesions, also diagnosed as "interstitial pneumonitis" by the roentgenologist, were found to be reversible in character in five of the six patients who could be followed. With the termination of the acute asthmatic attacks, resolution of the pulmonary infiltrations occurred. The eosinophile count in these cases ranged from 5 to 84 per cent.

In the remaining fourteen cases, roentgenograms revealed emphysema in two, lung cysts in two, and nothing abnormal in the other ten. The eosinophile count in this group was between 1 and 4 per cent.

Cardiac Manifestations.—The hearts of the patients under investigation were negative on auscultation, but tachycardia, ranging between 100 and 130 beats per minute, occurred during asthmatic attacks. Moderate enlargement of the left and right ventricles was found in one case (Case 10). This was confirmed by roentgenologic examination, which disclosed enlargement of the transverse diameter. The blood pressure in each case was normal. A maximum systolic pressure of as much as 140 was present in only four of the twenty cases.

The electrocardiographic abnormalities consisted of high P waves alone in six cases, and high P waves with QRS and T-wave deviations in nine others. In the remaining five cases the alterations were confined to the QRS and T waves only. The QRS changes included slurring, notching, and low voltage, and the T waves were low, isoelectric, or inverted.

In nine of the twenty cases the electrocardiographic abnormalities disappeared with the termination of the asthmatic paroxysm, whereas in five cases the changes persisted.

In the group with reversible electrocardiographic changes, two patients (Cases 1 and 2, Table I), showed alterations in the P wave only, four (Cases 7, 8, 9, and 13, Table I) had changes in the P waves, QRS complexes, and T waves, and three (Cases 16, 17, and 18, Table I)

TABLE I

CASE	PATIENT	SEX	AGE (YEARS)	FAMILY HISTORY OF ALLERGY	ETIOLOGY	DURATION OF ASTHMA	PHYSICAL EXAMINATION OF LUNGS	ROENTGENOGRAM OF CHEST	BLOOD EOSINOPHILES	PHYSICAL EXAMINATION OF HEART	BLOOD PRESSURE	ELECTROCARDIOGRAPHIC OBSERVATIONS
Group 1												
1	L. Z.	M	30	Asthma in maternal grandmother	Chronic sinusitis. Sensitivity to foods and inhalants	5 years	Occasional sibilant râles throughout both lungs	Interstitial infiltration, both lower lobes. Return to normal	5%	Negative	115/75	2/3/39. High wide P waves. Return to normal with subsidence of asthma
2	R. A.	F	18	Paternal uncle has hay fever	Chronic sinusitis. Sensitivity to pollens and foods	6 months	Sibilant and sonorous râles throughout	Negative	9%	Negative	125/70	3/21/39. Sinus tachycardia, rate 130. High P waves. Right axis deviation. Return to normal with subsidence of asthma
3	R. F.	M	42	Negative	Chronic sinusitis. Sensitivity to foods, pollens, and molds	13 years	Sibilant and sonorous râles throughout. Prolonged expiration	Large cyst at left base	3%	Negative	140/90	8/23/39. Sinus tachycardia, rate 110. High P waves. Unchanged after 8 months. 4/3/40
4	P. M.	M	24	Negative	Chronic sinusitis. Sensitivity to foods	2 years	Sibilant and sonorous râles throughout	Negative	8%	Negative	100/80	1/24/39. High P waves in Leads II and III. No follow-up
5	S. G.	F	39	Negative	Chronic sinusitis. Sensitivity to foods	34 years	Diminution of breath sounds, râles at bases	Infiltration about lipiodol deposits in lower lobes	3%	Negative	134/80	3/28/39. Sinus tachycardia, rate 130. High P waves. No follow-up

6	J. S.	M	51	Father had asthma; sister, urticaria	Chronic sinusitis. Sensitivity to foods and inhalants	30 years	Wheezing. Sibilant and sonorous râles throughout	Moderate pulmonary emphysema	0	Negative	140/82	4/7/39. Sinus tachycardia, rate 105. High P waves. No follow-up
						Group 2						
7	R. K.	M	20	Negative	Sensitivity to pollen and tobacco	8 months	Sibilant and sonorous râles throughout. Wheezing	Negative	7%	Negative	110/80	3/26/40. Sinus tachycardia. P waves high. QRS 1, 2, and 3 low. 5 minutes after adrenalin P wave small and inverted. Slight elevation of QRS 1 and 2. Slowing of heart rate
8	P. D.	M	41	Negative	Chronic sinusitis	3 years	Sibilant and sonorous râles. Wheezing	Interstitial infiltration. Return to normal	30 to 84%	Negative	125/80	8/1/35. Right ventricular preponderance. P waves high, QRS slurred. T_2 and T_3 inverted. 9/6/35. T_2 isoelectric. 11/16/35. T_1 higher, T_2 upright, EKG returning to normal
9	F. H	F	21	Negative	Chronic purulent sinusitis	5 years	Sibilant and sonorous râles throughout. Wheezing	Five recurrent attacks of interstitial pulmonary infiltration, migrating in various lobes of lung during a period of 4 years, returning to normal each time	35 to 50%	Negative	120/80	4/11/39. P waves high in Leads II and III. T_2 and T_3 low. 6/2/39. Leads I and II normal, Q_3 present. During an attack of polyarthritis, 9/10/40, sinus tachycardia, T waves low to semi-inverted. 11/1/40, T wave becoming upright

TABLE I—CONT'D

CASE	PATIENT	SEX	AGE (YEARS)	FAMILY HISTORY OF ALLERGY	ETIOLOGY	DURATION OF ASTHMA	PHYSICAL EXAMINATION OF LUNGS	ROENTGENOGRAM OF CHEST	BLOOD EOSINOPHILES	PHYSICAL EXAMINATION OF HEART	BLOOD PRESSURE	ELECTROCARDIOGRAPHIC OBSERVATIONS
10	G. R.	F	39	Son has asthma	Chronic sinusitis. Sensitivity to pollens and foods	2 years	Sibilant and sonorous râles. Wheezing	Negative	16%	Enlargement of the right and left ventricles confirmed by x-ray. No adventitious sounds	110/68	5/23/40. P waves high. QRS 1, 2, and 3, small and slurred. T_2 diphasic, T_3 inverted. Asthma and EKG changes persist.
11	S. B.	F	43	Father had asthma	Chronic sinusitis	4 years	Sibilant and sonorous râles throughout. Hyperresonant, prolonged expiration	Negative	0	Negative	100/80	5/12/39. P waves high. T_2 low, T_3 inverted. RS-T_2, RS-T_3 depressed. 7/20/39, six weeks later, P waves high. T waves and RS-T normal
12	R. M.	F	38	Negative	Chronic sinusitis	2 years	Sibilant and sonorous râles throughout. Wheezing	Cyst in right upper lobe	2%	Negative	120/70	2/6/39. Sinus tachycardia, rate 105. P waves high. QRS low. Tendency to R.A.D. Asthma and EKG changes persist

13	E. C.	F	42	Negative	Chronic sinusitis. Sensitivity to pollens and inhalants	28 years	Sibilant and sonorous râles throughout	Interstitial infiltration, right upper and lower lobes Return to normal	16%	Negative	105/80	3/25/41. Sinus tachycardia, rate 120. R-T segments depressed in Leads II and III. T_2 and T_3 diphasic. Right axis deviation. 4/11/41. Return to normal
14	G. S.	F	37	Negative	Chronic sinusitis	9 years	Sibilant and sonorous râles throughout	Interstitial infiltration of right lower lobe	9%	Negative	128/85	12/27/38. P wave high, QRS low. T_1, T_2, and T_3 low. No follow-up
15	S. G.	M	48	Negative	Chronic sinusitis	15 years	Emphysematous chest. Sibilant and sonorous râles throughout	Emphysema. Large blebs in both lungs	1%	Negative	120/80	6/17/36. Sinus tachycardia, rate 125. P waves high. Tendency to R.A.D. QRS low. No follow-up
						Group 3						
16	L. G.	F	48	Mother had asthma and hay fever	Chronic sinusitis	2 years	Wheezing. Sibilant and sonorous râles throughout	Acute interstitial infiltration in right upper lobe. Return to normal	26 to 47%	Negative	105/70	11/4/38. T_1 semi-inverted. T_2 and T_3 inverted. Two weeks later, when asthmatic attack had subsided, EKG became normal
17	F. R.	F	60	Negative	Chronic sinusitis	11 years	Wheezing, prolonged expiration. Sibilant and sonorous râles throughout. Emphysema	Heart enlarged to left	4 to 12%	Negative	120/74	7/28/39. Left axis deviation. QRS slurred, of low amplitude, in Lead II. R-T segment depressed in Lead I, elevated in Lead III; T_1 and T_3 low. Nine days later, when asthma subsided, EKG became normal

TABLE I—CONT'D

CASE	PATIENT	SEX	AGE (YEARS)	FAMILY HISTORY OF ALLERGY	ETIOLOGY	DURATION OF ASTHMA	PHYSICAL EXAMINATION OF LUNGS	ROENTGENOGRAM OF CHEST	BLOOD EOSINOPHILES	PHYSICAL EXAMINATION OF HEART	BLOOD PRESSURE	ELECTROCARDIOGRAPHIC OBSERVATIONS
18	A. H.	F	56	Negative	Chronic sinusitis. Sensitivity to foods and inhalants	3 years	Sibilant and sonorous râles throughout	Negative	4 to 8%	Negative	140/90	3/11/39. RS-T_2 depressed, T_2 diphasic. T_3 isoelectric. When asthma had subsided, EKG became normal
19	D. C.	F	38	Negative	Undetermined	11 years	Wheezing. Sibilant and sonorous râles throughout	Negative	2%	Negative	140/80	6/29/36. T_1 inverted. EKG taken between 2 asthmatic attacks. 9/8/36. Patient died in status asthmaticus
20	G. E.	F	48	Negative	Chronic sinusitis. Sensitivity to foods	3 years	Wheezing, prolonged expiration, crepitating râles throughout lungs	Emphysema. Lung cyst	4%	Negative	130/80	12/1/39. QRS low in all leads. T_2 low. T_3 inverted. 4/26/40. T_1, T_2 and T_3 isoelectric. Moderately severe asthma present

presented disturbances limited to the QRS and T waves. Despite the fact that the last three patients were the oldest in the series (45, 56, and 60 years of age, respectively), the myocardial disturbances responsible for their electrocardiographic abnormalities were reversible.

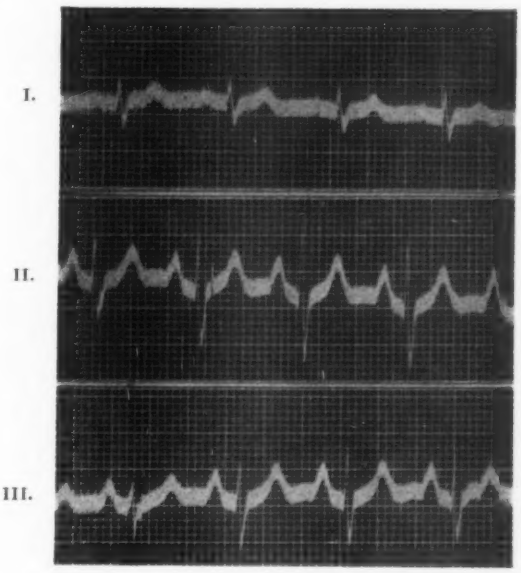


Fig. 1.—Case 4, Group 1. P. M., male, aged 24 years. Record taken Jan. 24, 1939, shows enlarged P waves in Leads II and III.

One of the five patients (Case 3) with irreversible changes showed persistent enlargement of the P waves only. This man had had asthma for thirteen years, together with pulmonary emphysema and a lung cyst. The other four patients presented changes in the P, QRS, and T waves. Of these, one patient (Case 10, Table I), aged 39, had enlargement of the right and left sides of the heart without demonstrable emphysema; a second (Case 11) had slight enlargement of the right side of the heart and moderate emphysema disclosed at autopsy; the third (Case 12) had evidence of right ventricular preponderance with marked emphysema and a lung cyst; and the fourth (Case 20), of group three, showed deviations limited to the QRS complexes and T waves, associated with continuous asthma, emphysema, and lung cyst.

The remaining six patients could not be classified as to reversibility or irreversibility of the changes because of inadequate follow-up studies. Of these, three (Cases 4, 5, and 6) showed high P waves only; two (Cases 14 and 15) presented changes in the P, QRS, and T waves; and one (Case 19) had deviations in the T waves only.

It is to be noted that, of the nine patients with reversible electrocardiographic changes, five had intercurrent, interstitial, pulmonary infiltrations. The latter, together with the electrocardiographic changes,

disappeared with the termination of the asthmatic seizures, but not simultaneously with every attack. Thus, in two (Cases 8 and 9 of Group 2), the electrocardiographic changes persisted while lesions in other tissues were appearing, although the asthma and pulmonary infiltrations had disappeared. The new developments in Case 8 consisted of polyneuritis and eosinophilic peritonitis. In Case 9 they were acute pericarditis on one occasion, and polyarthritis associated with a maculopapular erythematous eruption which persisted for three weeks, on another. With the termination of these various complications, the electrocardiograms returned to normal in both cases. Abnormal electrocardiograms during asthma-free intervals were also observed in Case 10. In this case no pulmonary lesions were observed during asthmatic attacks.

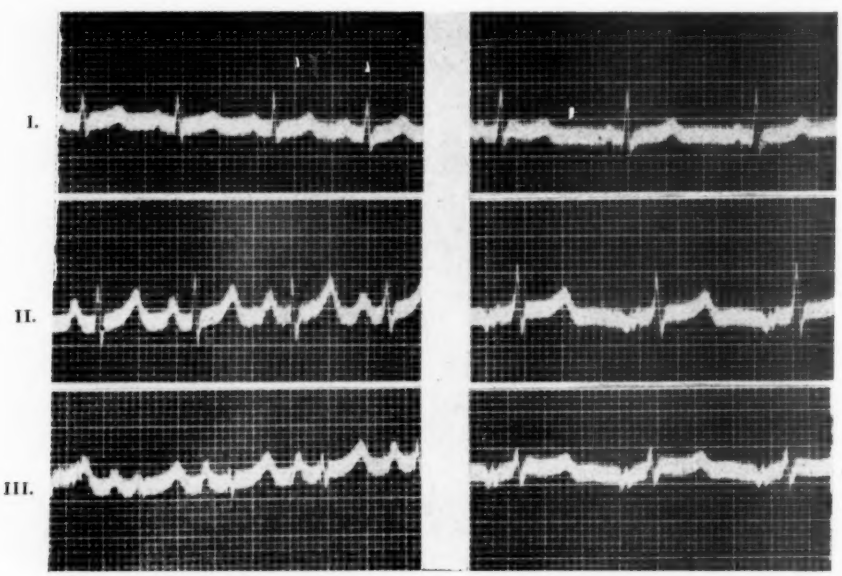


Fig. 2.—Case 7, Group 2. R. K., male, aged 20 years. *A*, record taken before administration of adrenalin, shows sinus tachycardia, high P waves, and low QRS. *B*, record taken five minutes after administration of adrenalin, shows slowing of rate, change in P waves, and higher QRS.

Studies of the arterial oxygen content by Dr. E. Somkin and Dr. A. Weiss in three of the cases (Cases 10 and 13 of Group 2, and Case 20 of Group 3) during the asthmatic attacks disclosed the following:

Patient 10, with irreversible electrocardiographic changes, showed an oxygen content of 18.65 volumes per cent and an oxygen capacity of 18.81 volumes per cent. The saturation was 99 per cent. Patient 13, who presented reversible electrocardiographic changes, showed an arterial oxygen capacity before an asthmatic attack, when her electrocardiogram was normal, of 20 volumes per cent and an oxygen content

of 18.23 volumes per cent, which gives 90 per cent saturation. During an attack she had an arterial oxygen capacity of 19.0 volumes per cent and an oxygen content of 17.0 volumes per cent, which also gives 90 per cent saturation.

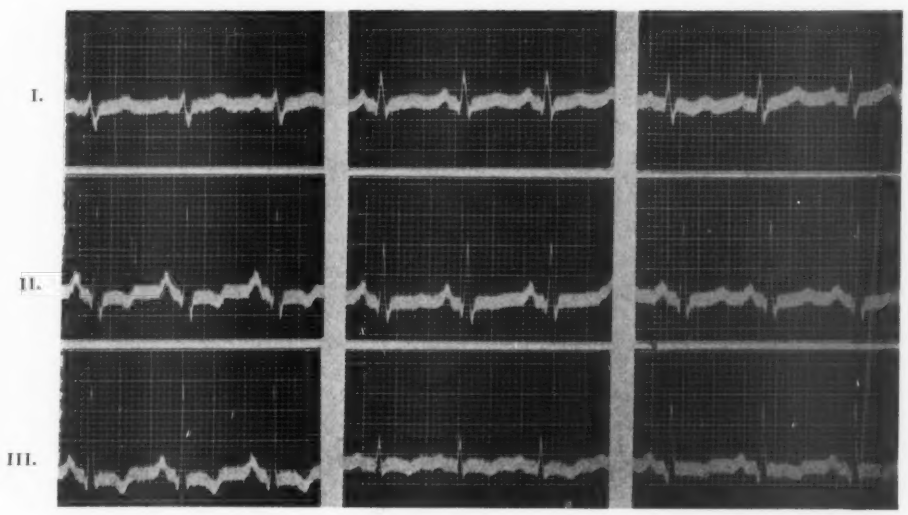


Fig. 3.—Case 8, Group 2. P. D., male, aged 41 years. *A*, record taken Aug. 1, 1935, shows tendency to R.A.D., high P waves, slurred QRS, and inverted T_2 and T_3. *B*, record taken Sept. 6, 1935, shows T_2 isoelectric. *C*, record taken Nov. 16, 1935, shows T_1 higher and T_2 upright.

Patient 20, who had chronic emphysema and a lung cyst, with irreversible electrocardiographic changes and cyanosis, showed an oxygen capacity of 22 volumes per cent and an oxygen content of 18.6 volumes per cent, indicating 84 per cent saturation.

No pertinent abnormalities referable to any other tissues were present in these cases, with the exception of nodular erythematous patches of the skin in Case 9 and reddish nodules in the conjunctivae in Case 10. Biopsy of the skin lesion in Case 9 disclosed perivascular eosinophilic infiltration, and the conjunctival nodules showed "collagen necrosis with an epithelioid giant cell reaction and marked infiltration with eosinophiles."

DISCUSSION

In evaluating the mechanism responsible for the various electrocardiographic changes, we considered (1) the effect of anoxemia, (2) the role of epinephrine, (3) positional changes of the heart, and (4) allergic responses in the lungs and heart.

1. *Anoxemia.*—Induced anoxemia in both experimental animals and man has resulted in prolongation of the P-R interval, alterations of the RS-T segment, and T-wave changes.[6-11] According to Tigges,[10] normal persons begin to show electrocardiographic changes at a stage

when signs of disturbances of consciousness present themselves. Levy, Barach, and Bruenn,[12] in a study of oxygen want in cases with cardiac pain, investigated one subject with a normal heart and noted slight flattening of the T waves in Leads I and II and a less deeply inverted T wave in Lead IV, after the inhalation of a 12 per cent oxygen mixture for twenty minutes. There was no effect on the R-T or S-T segments. The arterial oxygen saturation in this subject at the end of the experiment was 67.8 per cent. It would seem from such observations that in persons with normal hearts the oxygen want must be fairly severe before electrocardiographic changes begin to appear. The hearts of the patients studied were, with one exception, free of organic involvement.

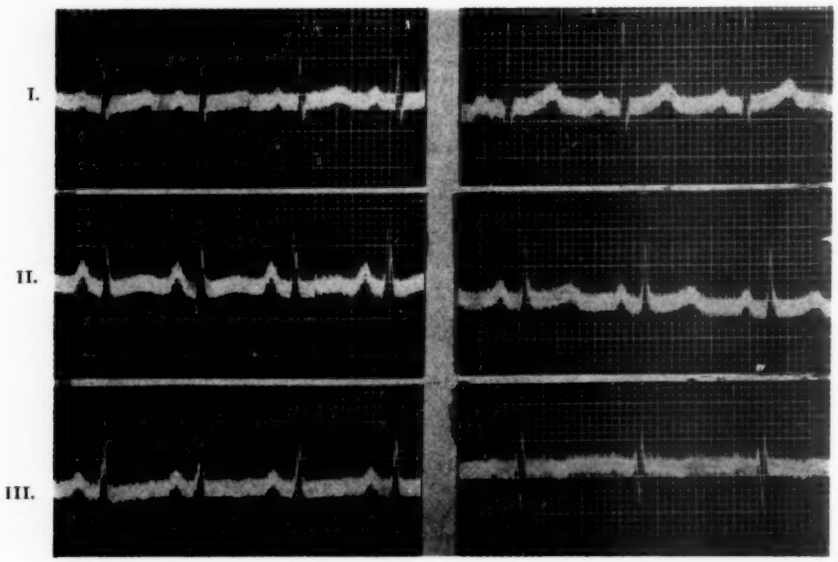


Fig. 4.—Case 9, Group 2. F. H., female, aged 23 years. *A*, record taken April 11, 1939, shows sinus tachycardia (rate 130), P wave high in Leads II and III, and T_2 and T_3 low. *B*, record taken June 2, 1939, shows normal Leads I and II and presence of Q_3.

The question of anoxemia in bronchial asthma has been dealt with by a number of investigators. In summarizing the observations up to 1929, Walzer,[13] quoting Wittkower, stated that, in the majority of cases, the oxygen saturation of the arterial blood is low, or at the lower threshold of normal, whereas the alveolar CO_2, the CO_2 combining power, and the pH of the blood are normal. This would indicate that there is no marked state of anoxemia in the uncomplicated cases of bronchial asthma. Meakins and Davies[14] found that, in certain types of asthma, accompanied by bronchitis, emphysema, and marked cyanosis, there was a varying degree of oxygen desaturation. There was no record of any electrocardiographic abnormalities in the cases which

they studied, and they concluded that the lowering of the arterial blood oxygen is directly proportional to the chronicity of the lesion and the extent of the emphysema and bronchitis. Their inability to increase the oxygen saturation of the blood to normal in certain instances by oxygen inhalation caused them to speculate concerning the possibility of underlying vascular involvement in these cases.

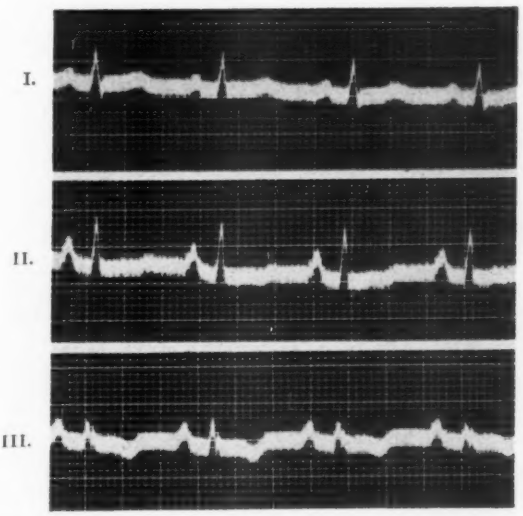


Fig. 5.—Case 10, Group 2. G. R., female, aged 39 years. Record taken May 23, 1940, shows P waves high, QRS low and slurred, T_2 diphasic, and T_3 inverted.

The majority of the patients under discussion were free from emphysema and any marked degree of cyanosis. As indicated, the only patient (Case 10) with demonstrable organic cardiac disease had an oxygen saturation during the asthmatic attacks of 99 per cent; in Case 13 it was 90 per cent, and, in Case 20, in which there were a fairly marked degree of cyanosis and roentgenologic evidence of moderate emphysema, accompanied by a lung cyst, 84 per cent. This last patient falls into the category described by Meakins and Davies.[14] It is conceivable that, under certain circumstances, when the myocardium is already affected, moderate degrees of anoxemia may contribute to the development of electrocardiographic abnormalities, but not necessarily be fundamentally responsible for them. A capacity for adaptation to a conspicuous degree of anoxemia without the development of any cardiac abnormalities is commonly noted in cases of asthma and emphysema.

2. *Epinephrine.*—Electrocardiographic changes after the administration of epinephrine have been attributed by Wiggers[15] and Fowler, Hurevitz, and Smith[16] to anoxemia of the myocardium resulting from constriction of the coronary vessels. In animals these alterations consist of directional changes in the T waves, "W" forms of the QRS

complexes, and elevation of the P-R segment.[17-19] The injection of epinephrine, however, is not always followed by constriction of the coronary vessels.[20, 21] According to Gollwitzer-Meier and Krüger,[22] epinephrine causes coronary dilatation.

Fig. 6.—Case 19, Group 3. D. C., female, aged 36 years. Record taken June 29, 1936, shows deep inversion of T_1.

In view of the fact that the effects of epinephrine injections on the electrocardiogram are transitory, and the records in our cases were often made during intervals when the patients were relatively comfortable, several hours after they had received epinephrine, it is questionable whether this drug had anything to do with the electrocardiographic changes which were noted. In Case 9 (F. H., Group 2), injections of epinephrine in oil twice daily to control residual wheezing after the subsidence of the acute attacks caused no abnormalities in the electrocardiogram, although changes in the auricular and ventricular complexes were present during the major asthmatic attacks. This is especially notable in view of the prolonged action of epinephrine in oil. In Case 7 (R. K., Group 2), in which high P waves appeared during an asthmatic attack, the administration of 0.3 c.c. of a 1:1,000 solution of epinephrine not only controlled the asthmatic paroxysm, but also caused reversion of the P wave to a normal level within five minutes. Repeated epinephrine injections in this patient while he was free of asthma had no effect on his electrocardiogram (Fig. 2).

3. *Positional Changes of the Heart.*—Master[23] and other investigators have reported low QRS waves in Lead I and right axis deviation in normal subjects with low diaphragms and mesially placed hearts. The roentgenograms of the twenty patients with electrocardiographic changes herein reported were reviewed. Only one patient showed a typically mesially placed heart. This patient had emphysema, a lung

cyst, and continuous asthma. In the remaining nineteen cases in this series, with the exception of Case 10, in which there was hypertrophy of the right and left ventricles, the hearts were of normal configuration. All the roentgenograms were taken while the patients were having asthmatic attacks.

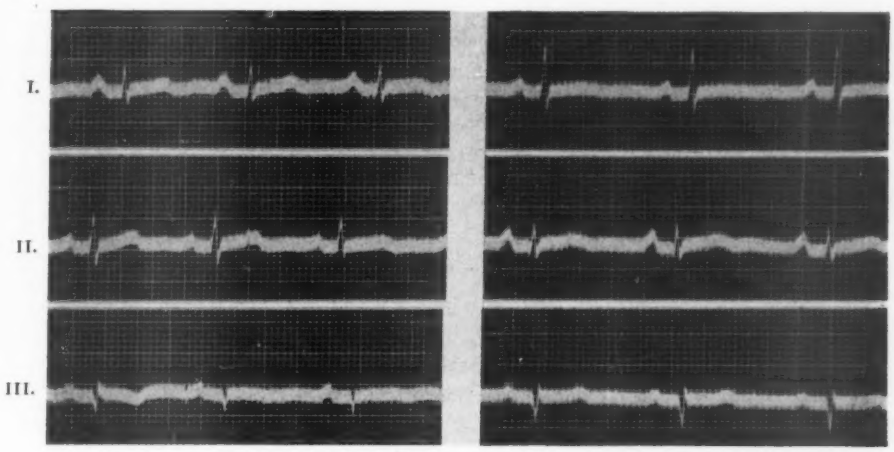


Fig. 7.—Case 20, Group 3. G. E., female, aged 48 years. *A*, record taken Dec. 1, 1939, shows QRS of low voltage. *B*, Record taken April 26, 1940, shows T_1 and T_2 lower.

The numerous allusions in the literature to a tendency toward right axis deviation in bronchial asthma may be attributed to positional changes as a result of a shift of the electrical axis toward the vertical plane. This, nevertheless, does not exclude the possible occurrence of right ventricular hypertrophy in cases of long-standing bronchial asthma, with frank right axis deviation in the electrocardiogram.

4. (*a*) *Allergic Response in the Lungs.*—A review of the pulmonary manifestations in the cases under investigation showed nothing in ten of the cases, interstitial infiltration in six, and emphysema and lung cysts in four.

In the ten cases in which no pulmonary lesions were demonstrable by roentgenologic examination, it may be assumed that the allergic reaction was essentially confined to the bronchi. Repeated attacks in such cases lead to hypertrophy of the bronchial musculature and various productive changes, including thickening of the bronchial blood vessels, as pointed out in autopsy studies by Huber and Koessler[24] and others. In the six patients with pulmonary infiltration, the development of the lesions was insidious in onset, and migratory, exudative, interstitial, and miliary in distribution, simulating tuberculosis. It was accompanied by fever ranging between 100° and 102° F., cough, asthma, and sputum eosinophilia. Often the changes in the lungs could not be detected on physical examination alone. Similar pulmonary infiltra-

tions, but without asthma, have been recorded by Löffler,[25] Engel,[26] Cole and Korns,[27] Vaughan and Hawke,[28] and others. Vaughan and Hawke, as well as Cole and Korns, regarded the pulmonary lesions in their cases as expressions of a more or less disseminated "angioneurotic edema" due to food allergy. The absence of asthma in the majority of the cases reported indicates that allergic inflammatory reactions in the lungs may occur independently of bronchial asthma, a fact which has been proved experimentally. Although the nature of the pulmonary lesions in our cases cannot be established unequivocally, the probability is that they represent hyperergic forms of response, in which interalveolar capillaries, the larger vessels, and the associated mesenchymal structures participate. The resultant interstitial edema and cellular infiltrations could account for the peculiar roentgenographic appearance and paucity of physical signs. In support of this view the following observations may be offered. First, the roentgenographic shadows were not homogeneous, like those produced by pneumonia; second, their miliary and interstitial character suggested a hematogenous rather than an alveolar distribution; third, their appearance with the outbreak and disappearance with the termination of the asthmatic paroxysm and sputum and blood eosinophilia suggested not only a reversibility common to allergic vascular reactions, as in urticaria, but also the participation of a common allergic excitant. Autopsy observations in two of a group of cases reported by one of us (J. H.)[1] in which there were similar clinical manifestations disclosed that the interstitial lesions in one patient, aged 11 years, consisted of cellular infiltration of the interalveolar septa with lymphocytes, eosinophiles, and polymorphonuclear cells, fibrosis, and edema, as well as arteritis of the pulmonary vessels. Other important organs were the seat of periarteritis nodosa. In the second patient, aged 36 years, the small vessels of the lung were thickened, and the vessels of the heart, pericardium, and liver showed evidence of periarteritis nodosa. Thickening of the pulmonary arterioles, giving rise in some places to endarteritis obliterans, was also reported by Kountz and Alexander[29] in a patient, aged 48, with long-standing asthma, who did not have diffuse hyperergic vascular disease. It would seem, therefore, that changes in the vascular system of the lungs in asthmatic patients may vary, not necessarily with the age of the patient, but with the tempo of the allergic process.

In cases in which the allergic tissue reactions recur, the erstwhile reversible process may become irreversible, and organization, with fibrous tissue formation appearing in the roentgenogram as interstitial fibrosis, may ensue. A comparable train of events results in the production of the so-called hyperplastic sinusitis, after repeated sinus attacks in chronic asthmatic patients. The pulmonary fibrosis may cause emphysema, as noted in two of the cases, and lung cysts probably

result from rupture and coalescence of emphysematous blebs; this was also evident in two other cases in this series.

4. (*b*) *Cardiac Reactions Following Sensitization.*—Numerous investigators have reported that electrocardiographic abnormalities occur in experimental animals during anaphylactic shock. These changes consisted of disturbances of conduction and abnormalities in the origin and spread of the electrical impulses. They have been attributed by some observers to anoxemia of the myocardium, and, by others, to toxic substances elaborated during the shock. Wilcox and Andrus[30] demonstrated various electrocardiographic abnormalities, including prolongation of the P-R interval, changes in the form of QRS complex, directional changes of the T wave, ectopic rhythms, and auriculoventricular dissociation, with ventricular tachycardia, when the perfused, isolated hearts of guinea pigs which had been sensitized to horse serum were exposed to small amounts of homologous antigen. These abnormalities were ascribed to coronary insufficiency because there was a striking reduction in the rate of coronary flow.

In the hearts of two patients who died during serum sickness, Clarke and Kaplan[31] found histologic changes which resembled those which occur in animals when protracted anaphylaxis is induced by foreign serum. These lesions were of a hyperergic nature, and consisted of proliferation of histiocytes in the intima of the large vessels and necrotizing arteritis and periarteritis of the smaller coronary arteries.

In view of these experimental and pathologic observations, the question arises whether the electrocardiographic abnormalities in certain cases of bronchial asthma may not represent allergic responses in the pulmonary and coronary vessels to the agents implicated in the production of the asthmatic seizures. Since, in the cases studied, neither epinephrine nor positional changes of the heart could be regarded as responsible for the electrocardiographic abnormalities, the problem becomes one of the relative roles of allergic reactions in the lungs and heart and associated anoxemia.

Despite the variations in the cardiac responses to oxygen want, the oxygen deficit which is necessary to produce electrocardiographic changes in normal subjects, as has been noted above, seems to be much greater than that commonly encountered in the average asthmatic patient with an intact heart. Observations on the arterial anoxemia in three of the cases did not indicate any high degree of oxygen unsaturation. Pending further investigation of arterial oxygen saturation (now in progress), definite conclusions as to the exact relationship between oxygen want and the electrocardiographic abnormalities in cases of asthma must be held in abeyance.

SIGNIFICANCE OF P-WAVE CHANGES

Inasmuch as the cardiac diseases which usually cause abnormalities of the P waves, such as mitral stenosis and congenital heart disease,

could be excluded, it may be assumed that the high voltage of the P wave in these cases depended on an extracardiac factor. In view of the fact that the high P waves appeared during asthmatic seizures and disappeared with their recession, they may be regarded as indicating that a transitory increase in the tension in the lesser circulation was associated with the asthmatic paroxysm. Since the latter was an allergic phenomenon, it would be reasonable to assume that the factors involved therein would likewise play a role in the augmentation of the vascular tension. Accordingly, the currently accepted theory of the mechanism involved in the allergic response, which implies the liberation of certain injurious agents of a histamine-like character on or within the tissue cells consequent upon an antigen-antibody interaction, may be utilized in explaining the phenomena observed. If we accept the contention of one group of investigators,[32, 33] who claim that the effect of histamine products is one of constriction of arterioles and dilatation of capillaries, associated with increased permeability, it is conceivable that, with the elaboration of such, or similar, substances during asthmatic attacks, spasm of the pulmonary arterioles, as well as increased dilatation and permeability of the interalveolar capillaries, may ensue. To this may be added contraction of the bronchi, which is another effect of histamine. If the constriction of the vessels is sufficiently marked it may interfere with the pulmonary circulation, and the tissue edema which results from the increased vascular permeability may act as a tamponade, and add to the burden of the pulmonary flow. The resulting obstruction to the circulation in the lung could give rise to hypertension of the lesser circulation. Such an increase of tension would augment the load of the right ventricle, and, when transmitted to the right auricle, would be reflected in the electrocardiogram by increased voltage of the P waves.

This sequence of events, namely, hypertension of the lesser circulation, followed by encroachment upon the integrity of the right side of the heart, finds its analogue in the spasmodic contraction of the pulmonary vessels and the resultant dilatation and failure of the right side of the anaphylactic rabbit's heart.

The high P waves disappeared in five of the cases when the attacks of bronchial asthma subsided, which suggests that the pulmonary vascular abnormalities are reversible. They likewise returned to normal in Case 7 (R. K., Group 2) after the administration of adrenalin. In this instance it may be assumed that the epinephrine relieved the tissue edema and the bronchospasm brought about by the released "H" substance, thus reducing the intra-auricular tension. The antagonism of epinephrine and histamine is well known.

Confirmatory evidence of pre-existing hypertension of the lesser circulation was obtained at the autopsy on S. B. (Case 11, Group 2), whose electrocardiogram had shown recurrently high P waves. This consisted of thickening of the walls of the pulmonary vessels and mod-

erate hypertrophy of both the right auricle and ventricle. It is significant that roentgenologic examination of this patient shortly before her death showed no gross abnormalities in the cardiac silhouette. Scarff,[34] who studied the effects of ligation of the left pulmonary artery in dogs, found a temporary increase of 30 to 50 per cent in the pulmonary systolic pressure, and 35 to 100 per cent in the diastolic pressure. These pressures subsequently returned to normal. Three or four months later, no increase in the size of the heart was detectable by the usual roentgenologic examination, although at autopsy the right ventricle was found to be distinctly heavier than normal. From these observations it would seem that the ordinary roentgenographic or fluoroscopic examination cannot disclose early, moderate changes in the size of the myocardium which would suggest, in the absence of the usual, known, responsible factors, an alteration in the tension in the pulmonary circulation. The presence of a high P wave, therefore, in the light of the experimental observations of Scarff and the autopsy observations in the case under discussion, must be regarded as *one of the earliest indications* of increased tension in the lesser circulation.

The persistence of high P waves in repeated electrocardiograms in Cases 3, 10, and 12 could be attributed to a permanent increase of tension in the lesser circulation caused by the emphysema and lung cysts which were demonstrated by clinical and roentgenologic examination in two of these patients. Inasmuch as the degenerative tissue changes which are associated with emphysema are usually combined with a reduction of the vascular bed, it may be inferred, in the light of our hypothesis, that the latter is a result of irreversible allergic reactions in the blood vessels of the lungs.

AURICULAR AND VENTRICULAR ELECTROCARDIOGRAPHIC CHANGES

Only one patient (Case 10) who had enlarged P waves, small and slurred QRS waves, and inversion of T_2 and T_3, showed roentgenologic evidence of right- and left-sided cardiac enlargement. In this case, hyperergic vascular disease, characterized by perivascular infiltration, with eosinophilia suggestive of the preliminary stages of periarteritis nodosa, was demonstrated in biopsy sections of a nodule in the conjunctiva. The persistence of the electrocardiographic abnormalities in this case during asthma-free intervals, as well as the permanent increase in the size of the heart, indicated that these changes were not dependent upon anoxemia caused by the asthmatic paroxysms, but, in all probability, reflected irreversible hyperergic responses in the coronary vessels to allergenic stimulation. Actual determination of the arterial oxygen tension of this patient's blood during one of her asthmatic seizures showed that it was 99 per cent saturated.

In contrast to these permanent alterations were the similar, but reversible, electrocardiographic changes in Cases 8 and 9 of this group. These patients likewise presented signs and symptoms of generalized

hyperergic vascular disease, which, however, did not progress with the rapidity and intensity as in Case 10, and tended toward remission. Thus, Patient 8, who presented the signs of periarteritis nodosa, became completely well while under observation, in spite of the peripheral neuritis, the eosinophilic peritonitis, and the subsequent intestinal infarction which was attributed to arteritis of one of the mesenteric vessels. The recovery, which was possibly temporary, probably occurred because the hyperergic vascular process was reversible. A similar favorable issue was observed in Case 9, with termination of the acute pericarditis, urticaria, and fugitive joint swellings. While the latter symptoms prevailed, the asthma which preceded their onset vanished, only to return with the recession of the pericarditis, urticaria, etc., illustrating a shift in shock organs which is common in allergic states. The electrocardiographic abnormalities which were originally ushered in with the asthmatic paroxysm remained unaltered during the development of symptoms in the other shock tissues. The restoration of the electrocardiograms to normal with the complete recovery of both of these patients signalized a remission of the allergenic stimulation which was basically responsible not only for the asthma, but also for the manifestations in the other organs. Thus the manner of development and the course of the symptoms in these three cases would tend to support the theory that the electrocardiographic changes were in all probability due to various degrees of allergic reactions in the coronary vessels, such as spasm and edema, with secondary ischemia of the myocardium, rather than the result of primary oxygen want associated with asthma. Except for the fact that the tissue responses in the other seventeen cases in this series were limited to the lungs and heart, the identity in symptomatology suggests a similar pathogenesis in the evolution of the pulmonary and electrocardiographic abnormalities.

VENTRICULAR CHANGES

It is well known that aberrations of the QRS complex and RS-T segments as well as T-wave changes, may result from pericardial involvement, myocardial damage brought about by local anoxemia consequent upon coronary artery constriction, such as is associated with coronary occlusion, or the direct toxic effects upon the myocardium of such systemic diseases as diphtheria or rheumatic fever. Since the ventricular electrocardiographic changes in many of our cases showed a direct temporal relationship to the occurrence and subsidence of both the asthmatic attacks and pulmonary infiltration, they may also be considered as manifestations of various degrees of allergic response in the vessels of the heart, with resultant coronary insufficiency and myocardial ischemia. Such a view, taking into consideration the theoretical explanation given above in respect to the allergic reaction, would also imply the mediation of a histamine-like substance. This

concept finds support in the investigations of Weiss, et al.,[35] who described T-wave changes in human beings after the intravenous administration of small doses of histamine solution, and also in the experimental observations of Ewert and Kallos[36] on guinea pigs after the inhalation of finely divided histamine. The inversion of T_1 in Case 19, of Group 3, may be interpreted as a manifestation of a mechanism similar to that described by these observers. On the day that the record was taken, this patient had no asthma and was devoid of any clinical manifestation of anoxemia. She left the hospital improved, only to return five weeks later in status asthmaticus. She died after an injection of morphine. Except for emphysema and right-sided cardiac dilatation, with hypertrophy, autopsy failed to disclose any gross changes in the myocardium or coronary vessels. Microscopic examination, however, showed scattered foci of myofibrosis in the left ventricle and perivascular fibrosis at the apex, in addition to endocardial thickening of the left auricle. Similar lesions have been observed in coronary insufficiency in patients with narrowed but patent arteries, as well as after certain systemic infections.* In the absence of either of these factors the possibility that the allergens responsible for the asthmatic attacks may have acted through the mechanism of a histamine release upon the coronary vessels and capillaries, giving rise to the electrocardiographic changes, as well as the histologic lesions, should not be dismissed.

CONCLUSIONS

In summarizing these various observations the following deductions seem to be pertinent.

There was no clinical indication or laboratory evidence from study of the oxygen saturation of the blood in three cases of this group that respiratory anoxemia was the primary factor in inducing the electrocardiographic changes which were observed. Moreover, the relative unimportance of respiratory anoxemia was also illustrated by the fact that, in Cases 8, 9, and 10, the electrocardiographic abnormalities persisted during asthma-free periods, when hyperergic manifestations were developing in other shock tissues. The temporal relationship between the appearance and disappearance of the pulmonary lesions, the electrocardiographic changes, and the involvement of various other shock organs implies a common underlying mechanism. Although there was no involvement of shock tissues other than the heart and lungs in the remaining cases, the common association of electrocardiographic disturbances and pulmonary involvement with asthma, the same as in Cases 8, 9, and 10, suggests a similar pathogenesis.

The simultaneous occurrence of deviations in the auricular and ventricular complexes may be explained in two different ways:

*Personal communication from Dr. Henry Horn.

(a) They may be caused by coronary insufficiency, brought about through compression of the right coronary artery because of a rise in intraventricular pressure[37] consequent upon an increase in tension in the lesser circulation. The latter may be considered the result of allergic vascular reactions in the lung. Such a mechanism could account for the high P waves, as well as changes in the QRS and T waves. These changes would necessarily be reversible, and be dependent on the presence or absence of hypertension in the pulmonary circuit and the asthmatic paroxysms.

(b) They may indicate not only hypertension of the lesser circulation, but also the development of allergic reactions in the coronary vessels, such as spasm and edema, leading to insufficiency. The reversibility or irreversibility of the electrocardiographic deviations would therefore depend on the character of the exciting agent and the intensity and extent of the allergic response.

SUMMARY

1. Twenty of a series of fifty patients with bronchial asthma presented electrocardiographic abnormalities, such as tachycardia, axis deviation, high P waves, and QRS, RS-T, and T-wave changes.

2. Pulmonary infiltration appeared during the asthmatic paroxysms in six cases and disappeared in five. These infiltrations were regarded as manifestations of allergic reactions in the vessels and interstitial tissues of the lung.

3. The electrocardiographic abnormalities were reversible in nine cases and irreversible in five. The remaining six patients could not be followed. The reversible electrocardiographic changes appeared and disappeared in the majority of cases at the same time as the pulmonary lesions and asthmatic attacks.

4. The simultaneous occurrence of the pulmonary and cardiac changes suggested a common pathogenesis.

5. Changes in the auricular complexes, characterized by an increase in the voltage of the P waves, were present in fifteen cases. These were interpreted as indicating increased intra-auricular tension secondary to hypertension of the lesser circulation brought about by allergic reactions in the vessels of the lung similar to rabbit anaphylaxis.

6. Electrocardiographic abnormalities in the ventricular components were observed in fourteen cases. They were reversible in eight cases and irreversible in three. The remaining patients could not be kept for observation. The occurrence of these abnormalities in three cases during asthma-free intervals indicated that they were independent of respiratory anoxemia. That they may have been due to hyperergic reactions in the coronary vessels is highly probable, in the light of the clinical course. This was indicated by the involvement of numerous

shock tissues of a vascular nature, and the perivascular eosinophilic infiltration found in the biopsy sections of the conjunctiva in Case 10 as well as similar lesions in the skin of Case 8.

REFERENCES

1. Harkavy, Joseph: Vascular Allergy; Pathogenesis of Bronchial Asthma With Recurrent Pulmonary Infiltrations and Eosinophilic Polyserositis, Arch. Int. Med. **67**: 709, 1941.
2. Kahn, M. H.: The Electrocardiogram in Bronchial Asthma, Am. J. M. Sc. **173**: 555, 1927.
3. Unger, L.: Electrocardiographic Study of the Heart in Bronchial Asthma, J. Allergy **2**: 17, 1930.
4. Criep, L. H.: Effect of Bronchial Asthma on the Circulation, Arch. Int. Med. **49**: 241, 1932.
5. Colton, W. A., and Ziskin, T.: The Heart in Bronchial Asthma, J. Allergy **8**: 347, 1937.
6. Kountz, W. B., and Gruber, C. M.: The Electrocardiographic Changes in Anoxemia, Proc. Soc. Biol. & Med. **27**: 170, 1929.
7. Kountz, W. B., and Hammouda, M.: Effect of Asphyxia and of Anoxemia on the Electrocardiogram, AM. HEART J. **8**: 259, 1932.
8. Rothschild, M. A., and Kissin, M.: Production of Anginal Syndrome by Induced General Anoxemia, AM. HEART J. **8**: 45, 1933.
9. Katz, L. N., Hamburger, W. W., and Schutz, W. J.: Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects. Its Bearing on the Mechanism of Attacks of Angina Pectoris, AM. HEART J. **9**: 771, 1934.
10. Tigges, F.: Das Electrokardiogramm bei Hypoxämie, Ztschr. f. Kreislaufforsch. **28**: 225, 1936.
11. Green, C. W., and Gilbert, N. C.: Studies on the Responses of the Circulation to Low Oxygen Tension. III. Changes in the Pacemaker and in Conduction During Extreme Oxygen Want as Shown in the Human Electrocardiogram, Arch. Int. Med. **27**: 517, 1921.
12. Levy, R. L., Barach, A. L., and Bruenn, H. G.: Effects of Induced Oxygen Want in Patients With Cardiac Pain, AM. HEART J. **15**: 187, 1938.
13. Walzer, M.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., 1931, Charles C Thomas.
14. Meakins, J. C., and Davies, H. W.: Respiratory Function in Disease, London, 1925, Oliver & Boyd.
15. Wiggers, C.: Physiology in Health and Disease, Philadelphia, 1935, Lea & Febiger.
16. Fowler, W. M., Hurevitz, H. M., and Smith, F. M.: Effect of Theophylline Ethylenediamine on Experimentally Induced Cardiac Infarction in Dogs, Arch. Int. Med. **56**: 1242, 1935.
17. Kahn, R. H.: Die Störungen der Hertztätigkeit durch Adrenalin in Elektrokardiogramm, Arch. f. d. ges. Physiol. **129**: 379, 1909.
18. Milles, G., and Smith, P. W.: Effects of Epinephrine on the Heart, AM. HEART J. **14**: 198, 1937.
19. Rosenblum, H. H., Hahn, R. G., and Levine, S. A.: Epinephrine, Its Effect on Cardiac Mechanism in Experimental Hyperthyroidism and Hypothyroidism, Arch. Int. Med. **51**: 279, 1933.
20. Anrep, G. V., Barsoum, G. S., and Talaat, M.: Liberation of Histamine by the Heart Muscle, J. Physiol. **86**: 431, 1936.
21. Melville, K. I.: Direct Observations of the Influence of Various Coronary Dilator Agents Upon Coronary Constriction Produced by Pituitary Extract, Arch. internat. de pharmacodyn. et de thérap. **44**: 316, 1933.
22. Gollwitzer-Meier, K., and Krüger, E.: Einfluss des Sympathicus auf die Coronargefässe, Arch. f. d. ges. Physiol. **236**: 594, 1936.
23. Master, A. M.: The Electrocardiogram and X-Ray Configuration of the Heart, Philadelphia, 1939, Lea & Febiger.
24. Huber, H. L., and Koessler, K. K.: The Pathology of Bronchial Asthma, Arch. Int. Med. **30**: 689, 1922.
25. Löffler, W.: Zur Differential-Diagnose der Lungeninfiltrierungen; über flüchtige Succedan-Infiltrate (mit Eosinophilie), Beitr. z. Klin. d. Tuberk. **79**: 368, 1932.
26. Engel, D.: Zur Frage des anaphylaktischen Frühjahrsödems der Lunge. Bemerkungen zu einer Arbeit von W. Löffler über dieses Thema, Beitr. z. Klin. d. Tuberk. **89**: 323, 1935.

27. Cole, J., and Korns, H. M.: Visceral Manifestations of Angioneurotic Edema. Report of a Case With Recurrent Pulmonary Involvement, J. Allergy **5**: 347, 1934.
28. Vaughan, W. T., and Hawke, E. K.: Angio-neurotic Edema With Some Unusual Manifestations, J. Allergy **2**: 125, 1931.
29. Kountz, W. B., and Alexander, H. I.: Death From Bronchial Asthma, Arch. Path. **5**: 1003, 1928.
30. Wilcox, H. B., and Andrus, E. C.: Anaphylaxis in the Isolated Heart, J. Exper. Med. **67**: 169, 1938.
31. Clark, E., and Kaplan, B. I.: Endocardial Arterial and Other Mesenchymal Alterations Associated With Serum Disease in Man, Arch. Path. **24**: 458, 1937.
32. Gaddum, J. H., and Holtz, P.: Localization of the Action of Drugs on the Pulmonary Vessels of Dogs and Cats, J. Physiol. **77**: 139, 1933.
33. Mauntner, H., and Pick, E. P.: Über die durch shoekgifte erzeugten Zirkulations-veränderungen, Arch. f. exper. Path. u. Pharmakol. **142**: 271, 1929.
34. Scarff, J. E.: Pulmonary Blood Pressures; an Experimental Study, Arch. Surg. **12**: 591, 1926.
35. Weiss, Soma, Robb, P., and Ellis, L. B.: The Systemic Effects of Histamine in Man, Arch. Int. Med. **49**: 360, 1932.
36. Ewert, B., and Kallos, P.: Elektrokardiographische Untersuchungen im experimentell hervorgerufenen Asthmaanfall der Meerschweinchen, Cardiologia **2**: 147, 1938.
37. Gregg, D. E.: The Phasic Blood Flow and Its Determinants in the Right Coronary Artery, Am. J. Physiol. **119**: 580, 1937.

Department of Clinical Reports

RECENT MYOCARDIAL INFARCTION FOLLOWED BY INVOLVEMENT OF THE JOINTS OF THE HAND AND WRIST

A Report of Three Cases

Joseph C. Meyer, M.D., and Herbert F. Binswanger, M.D.
Chicago, Ill.

THREE cases in which myocardial infarction was followed by unusual involvement of the joints, particularly of the right hand and wrist, were seen by us recently. Since we have been unable to find any report of a similar sequence of events, we desire to draw attention to it because it may be more than coincidental.

CASE REPORTS

Case 1.—H. R., a 53-year-old, married, white man, with a history of arthritis and rheumatism thirty years earlier, first noted attacks of dyspnea and precordial pain while on a trip to California. He remained in bed for one week, and, on his return home a week later, again complained of the same symptoms, which had increased in severity. He was hospitalized immediately. On admission, his temperature was 97.2° F.; his pulse rate, 88; his respiratory rate, 32; and his blood pressure, 96/78. Both the pulse and respirations were irregular. Physical examination revealed that the patient was pale and dyspneic; he was complaining of pain over the precordium. The heart was enlarged to the left on percussion; there were no cardiac murmurs; and the heart tones were of good quality. The lungs were normal. The liver was 3 fingerbreadths below the costal margin. Further physical examination revealed no abnormalities.

During the next few days he was markedly dyspneic and cyanotic, and had Cheyne-Stokes breathing. His temperature rose as high as 102° F., and the leucocyte count rose to 13,500. The blood pressure remained about 104/80. The electrocardiogram showed evidence of a recent anterior myocardial infarction in the healing stage. His convalescence was complicated by occasional attacks of precordial pain. There was present at this time a diffuse apex beat which suggested cardiac aneurysm, but this could not be confirmed by fluoroscopic examination.

Eight weeks after the onset of his myocardial infarction, he suddenly developed, for the first time, pain in the right metacarpophalangeal and carpal joints, associated with stiffness and swelling, but without redness or local heat. He was unable to flex the joints or to approximate the thumb to the little finger. Subsequently the right shoulder became involved, with pain, slight swelling, and limitation of motion. A month after the onset of the swelling in the right hand, a similar condi-

From the Cardiovascular Department, Michael Reese Hospital, Chicago.
Aided by the A. D. Nast Fund for Cardiac Research.
Received for publication Nov. 15, 1940.

tion developed in the left hand, although to a lesser degree, and involved principally the fingers. The recovery of the left hand was more rapid than that of the right. The swellings were treated with local heat and Crowe's vaccine. About eight months after the beginning of these joint symptoms he had improved sufficiently to drive his own car. He died suddenly two months later. No autopsy was performed.

CASE 2.—M. D., a 55-year-old, married, white man, with an essentially negative past history except for extrasystoles intermittently during the preceding ten years, and two attacks of renal colic within the preceding two years, was suddenly seized with an attack of severe, squeezing pain across the chest. Examination at this time revealed a pulse rate of 92 and a blood pressure of 160/110. The electrocardiogram two days later showed definite changes as compared with a curve taken five years before, and, with subsequent curves, suggested posterior myocardial infarction. There were continued fever up to 102° F. and a leucocytosis, accompanied by a fall in blood pressure to 80/60; the clinical manifestations were therefore also suggestive of myocardial infarction. The blood Wassermann and Kahn reactions were negative. During his convalescence, while at rest in bed, he had repeated attacks of precordial distress, together with paroxysmal auricular fibrillation; the latter was controlled with quinidine. After one such attack he developed pain in the right side of the chest, with râles at the right base posteriorly, which was thought to be caused by pulmonary infarction.

Two months after the beginning of the myocardial infarction, pain, swelling, and limitation of motion appeared in the small joints of the right hand and wrist. No redness, local heat, or systemic reaction accompanied the swelling. These signs in the right hand persisted for four months, subsiding gradually. Because of the diffuse apex beat and cardiac enlargement to the left on percussion, aneurysm of the ventricle was suspected, although this could not be confirmed fluoroscopically. He had occasional attacks of precordial distress for the next six months, but there was no recurrence of the swelling and stiffness of the right hand. He died suddenly while on a business trip, twelve months after the onset of his myocardial infarction. No autopsy was performed.

CASE 3.—B. L., a 72-year-old, white woman, had a history of frequent attacks of pain in various joints, including the shoulders and wrists, and showed roentgenologic evidence of hypertrophic arthritis of the cervical and dorsal spine. She had had hypertension for at least ten years. Her present difficulty began with a sudden attack of precordial pain, radiating down the right arm and associated with nausea, vomiting, and a fall in blood pressure. The temperature was 100.6° F., and the leucocyte count, 12,000. Râles were present at the bases of the lungs. She continued to have frequent attacks of pain over the precordium while at rest in bed. The electrocardiograms confirmed the clinical impression of myocardial infarction. Pain and swelling of the right carpal and metacarpal joints, without redness or local heat, developed six weeks after the onset of this attack. Soon the left hand was similarly involved, but to a lesser degree. During the height of the swelling there was marked limitation of motion. In the next five months the swellings of the hands gradually subsided, with the aid of local heat and massage. A year and a half later she developed another attack of severe substernal pain, typical of myocardial infarction, which led to her death in three days. No autopsy was performed.

DISCUSSION

These cases were striking in that the principal involvement occurred in similar joints in all three, and with about the same latent period after the onset of the myocardial infarction. Clinically, the process

resembled a periarthritis or fibrositis, rather than an intra-articular arthritis. The phalangeal and metacarpal joints were mainly involved; the carpal joints were affected to a lesser extent. The tissues about the joints became slightly fibrosed and tight to a rather uniform degree. The skin overlying the joints was tense and glistening, but not reddened. Flexion was very difficult. In each case the pain associated with the acute cardiac attack radiated down the right arm, although in one instance it also radiated down the left arm, but with less severity. In no case was there any history of previous involvement of the affected parts by a similar process, but in two cases there was a past history of arthritis and rheumatism.

One can only speculate as to the etiology. In cases in which joint symptoms occurred shortly after the myocardial involvement, Libman[1] refers to the toxic effect of the necrosis on joints which were perhaps sensitized by gout or some other cause. In our cases the latent interval between the infarction and the joint involvement seems too long for this explanation. Libman[2] also refers to underlying metabolic disorders and suggests that sensitization of the joints by such disorders may play a role in the pathogenesis of this phenomenon. Two of our patients had a history of arthritic attacks in various joints. Edeiken and Wolferth[3] refer to shoulder pain after myocardial infarction and suggest an analogy to causalgia, although in their cases there was no evidence of trophic or vasomotor changes. Our patients did show what may have been a trophic disturbance. Edeiken and Wolferth refer to Howard,[4] who reported periarthritis of the shoulder in cases of cardiac pain. Boas and Levy[5] reported cases of shoulder pain associated with angina pectoris and mycardial infarction. They suggest that sensitization of a dermatome by another disease might perhaps determine the site of radiation of pain. Summation of previous slight pain, plus cardiac pain, may be a factor. Extracardiac lesions, such as dental abscesses or spondylitis, are known often to determine the site of radiation of anginal pain.

It was noted in all our cases that the pain during the acute attack radiated down the right arm, which was the principal extremity involved. The possibility of a trophic disturbance following reflex vasomotor changes caused by the radiation of pain down the extremity has to be considered. The severe pain in the right arm may have contributed to subsequent inactivity and lack of use. Prolonged disuse will cause fibrosis about a joint, followed by bone and joint atrophy.[6] Atrophic changes in bones and in attachments about joints caused by lack of use have often been described.[7] Sudeck[8] attributed acute bone atrophy resulting from trauma to a reflex neurotrophic phenomenon.

The question of gout comes to mind. It is established that the orifices of the coronary arteries are frequently found to be occluded by atheromatous processes in cases of gout.[9] Unfortunately, however, neither

roentgenograms nor blood uric acid studies are available. It is hoped that such studies will be made in future cases.

The fact that all these patients died within a year of the acute cardiac attacks makes one wonder if any prognostic significance is to be attached to this sequence. These cases, coming so close to one another, have aroused our interest, and we are reporting them in the hope that others who may see similar cases may obtain further information, as we expect to do, to make possible better judgment of the prognosis and a better idea of the mechanisms involved in the syndrome.

We wish to express our thanks to Dr. Louis N. Katz for his suggestions in preparing this report.

REFERENCES

1. Libman, E.: Personal Communication.
2. Libman, E.: Discussion of paper by Boas and Levy,[5] AM. HEART J. **14:** 495, 1937.
3. Edeiken, J., and Wolferth, C. C.: Persistent Pain in Shoulder Region Following Myocardial Infarction, Am. J. M. Sc. **191:** 201, 1936.
4. Howard, T.: Cardiac Pain and Periarthritis of the Shoulder, M. J. & Rec. **131:** 364, 1930.
5. Boas, E. P., and Levy, H.: Extracardiac Determinants of the Site and Radiation of Pain in Angina Pectoris With Special Reference to Shoulder Pain, AM. HEART J. **14:** 540, 1937.
6. Allison, N., and Brooks, B.: Bone Atrophy, Surg., Gynec. & Obst. **33:** 250, 1921.
7. Gurd, F. B.: Functional Disabilities After Simple Fractures, Surg., Gynec. & Obst. **66:** 489, 1938.
8. Sudeck, P.: Ueber die acute entzündliche Knochenatrophie, Arch. f. klin. Chir. **62:** 147, 1900.
   Quoted by Key, J. A.: Local Bone Atrophy, Am. J. Roentgenol. **30:** 34, 1933.
9. McPhedran, W. F.: Gout. Tice, Practice of Medicine **9:** 22, 1938.
10. Askey, John: Personal Communication. Dr. Askey has written to us, telling of twenty-two similar cases in which there was an associated shoulder disability usually preceding the hand involvement. These cases have recently been reported in this journal.

CORONARY DISEASE IN THE APE

G. W. MANNING, M.D., TORONTO, CANADA

FOX[1] and Cowdry[2] have discussed general arteriosclerosis, including a brief description of coronary artery sclerosis in the higher monkeys and apes. Fatal coronary thrombosis, however, does not appear to have been observed. Consequently, the sudden death of an ape, shown at autopsy to have been caused by coronary thrombosis, is of particular interest in that it illustrates that coronary artery disease in the ape can progress to actual thrombosis, with sudden death, in a manner comparable to that observed in man. The history and post-mortem observations in a case of coronary thrombosis in an 8-year-old female ape are presented in this report.

CASE REPORT

History.—"Lizzie," prior to her sudden death, was apparently in good health; she was well developed, was well nourished, and had always been quite active. She was a pleasant, intelligent ape and the favorite of the keeper. She had not suffered from any illness prior to Nov. 23, 1939. There was no history of previous falling or shortness of breath. Menstruation had been regular and normal for the preceding two years. Although she copulated regularly and frequently, she had never become pregnant.

On the morning of November 23, Lizzie was sitting on her platform about 6 feet above the cage floor. She had refused her usual morning treat, a stewed fig. The keeper was leaving the cage when he heard a terrific din, and turned to see Lizzie howling and then fall to the floor of the cage, where she rolled over on her back, breathing with great difficulty. The dyspnea became progressively more severe; the animal died in about six minutes, with some terminal, isolated, spasmodic gasps.

Post-Mortem Examination.—The body was that of a large, well-developed ape. With the exception of the chest, the examination revealed nothing of interest. Examination of the uterus revealed that she was not pregnant at the time of death. When the chest was opened, the lungs appeared dark and heavy. There was no free fluid or blood in the pleural cavity. The heart and lungs were removed together. There was no gross evidence of necrosis, cavitation, or tuberculous disease in the lungs. The parenchyma was resistant to cutting, and the raw surface was moist. Pressure on the lung tissue expressed somewhat frothy, pink fluid into the bronchi and on to the cut surface. Examination of the pulmonary arteries revealed no gross evidence of embolism.

The pericardium was slightly dull in appearance. When the pericardial sac was opened, a moderate amount of unclotted, bloody fluid was found. The heart appeared soft and slightly enlarged. The anterior surface was fresh and glistening, with a considerable accumulation of fat toward the base. The posterior surface of the left ventricle showed a definite abnormality. In one area (Fig. 1) the peri-

From the Department of Medical Research, Banting Institute, University of Toronto.

Received for publication Nov. 15, 1940.

cardium was adherent to the heart muscle, but, by careful dissection of the granulation tissue which had formed (a few fibrous strands had to be divided), a large infarcted area was revealed. The heart measurements were as follows:

Width at base of ventricle	10.0 cm.
Length (apex to A-V sulcus)	7.8 cm.
Diameter of aorta	1.3 cm.
Diameter of pulmonary artery	1.3 cm.

The infarct, which measured 4.5 cm. by 2.5 cm., was soft and elevated. It had the appearance of fleshy granulation tissue superimposed on a fibrous base and surrounded by similar, but older, scar tissue. On cutting, the older infarct was found to be quite superficial. Just proximal to this area a recent hemorrhagic infarct was seen.

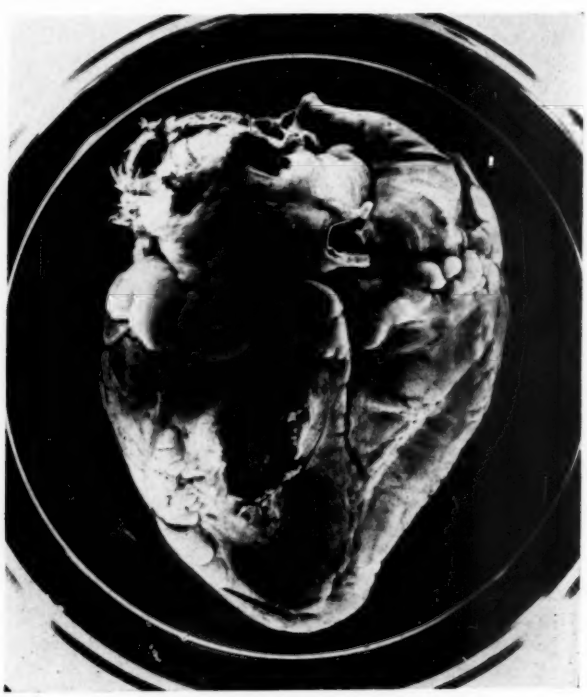


Fig. 1.—Posterior surface of heart.

The coronary arteries were injected with a calcium carbonate, linseed oil mass, which ran into the arteries readily with a little pressure, and was observed to flow into the large veins within a few seconds. When slightly more pressure was applied, the mass flowed freely into the left ventricle. Following this, a careful dissection of the coronary arteries was carried out. As the injection mass traveled along the circumflex branch of the left coronary artery it ran out into the heart muscle in the area of the recent infarct. The coronary artery leading to this area was readily opened, and, in the gross, did not appear to be atheromatous or narrowed. However, at the margin of the infarcted area the artery could no longer be traced as a single channel, but was found to be ruptured, allowing the injection mass to flow freely into the heart muscle. There was a wide separation of the muscle fibers in this area, indicating that the recent infarct had extended throughout the entire

thickness of the posterior ventricular wall. The myocardium in this area was soft and friable. The injection mass was scattered throughout this region, and no definite outline could be found. In general, this area appeared to be roughly oval, and about 2 cm. by 4 cm. in size. The endothelium of the remaining coronary arteries appeared smooth and glistening; there was no gross evidence of thickening, narrowing, or atheromatous changes.

Microscopic Observations.—Sections were taken from the liver, lungs, and numerous areas of the heart. There was marked congestion of the lungs. The blood vessels were engorged, and, in many areas, the bronchi were filled with a mixture of erythrocytes and pale-staining fluid (Fig. 2). The bronchial mucosa appeared thickened and edematous.

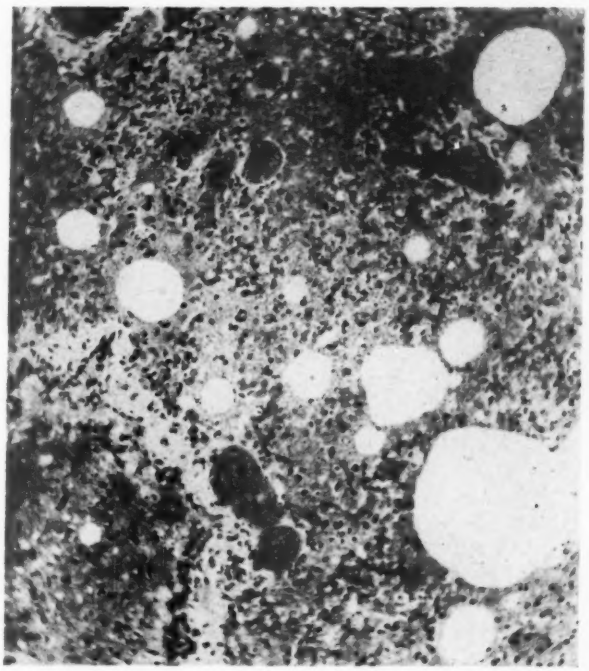


Fig. 2.—Photomicrograph of section of lung.

Sections taken from the liver showed evidence of acute congestion. In many areas there was hemorrhage in the central vein areas. Venous congestion in the portal areas was also found.

Microscopic examination of the older infarcted area on the posterior surface of the heart revealed a superficial area of granulation tissue, superimposed on fibrous tissue. The deeper branches of the coronary artery in this area were completely occluded by fibrous tissue (Fig. 3). In the area of the recent infarct (Fig. 4) there was a wide separation of the muscle fibers, resulting from the marked extravasation of blood. (Since the heart was perfused, few, if any, erythrocytes could be seen in this area.)

Further evidence of coronary artery disease was manifested, both in this area and other sections taken from the heart, by a considerable degree of intimal thickening. Subendothelial proliferation could be seen, particularly in the medium and smaller coronary arteries (Fig. 5), resulting in narrowing of the lumen.

Fig. 3.—Photomicrograph of scarred area shown in Fig. 1. Note complete occlusion of coronary arteries and fibrous tissue at lower part of figure, deep to the superficial scarred area.

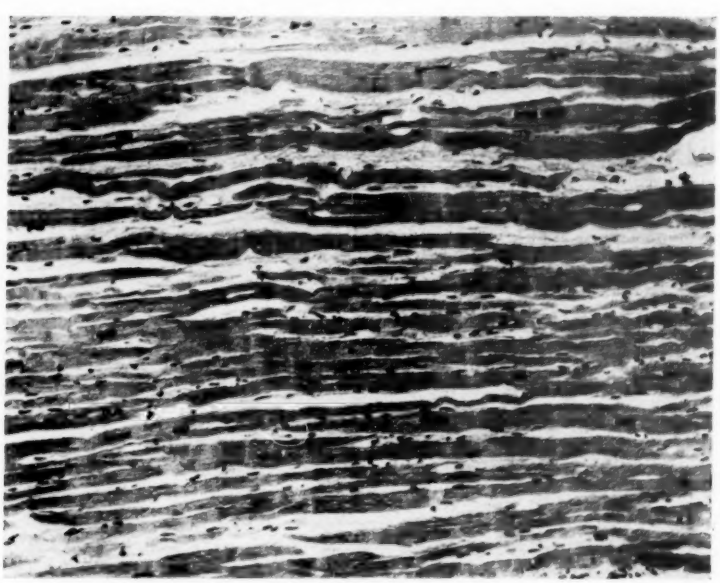


Fig. 4.—Section taken from freshly infarcted area.

DISCUSSION

The gross and microscopic examination of the heart would indicate that this ape had had coronary artery disease prior to her sudden "cardiac" death. This view is supported by the fact that there were an area of myocardial fibrosis, a recent infarct, and evidence of intimal thickening of the coronary arteries. A reasonable sequence of events would appear to be that coronary artery disease, with intimal thickening, had progressed in this heart until, because of either marked narrowing or thrombus formation, an area of fibrosis occurred about the termination of a branch of the left circumflex coronary artery. Later, more

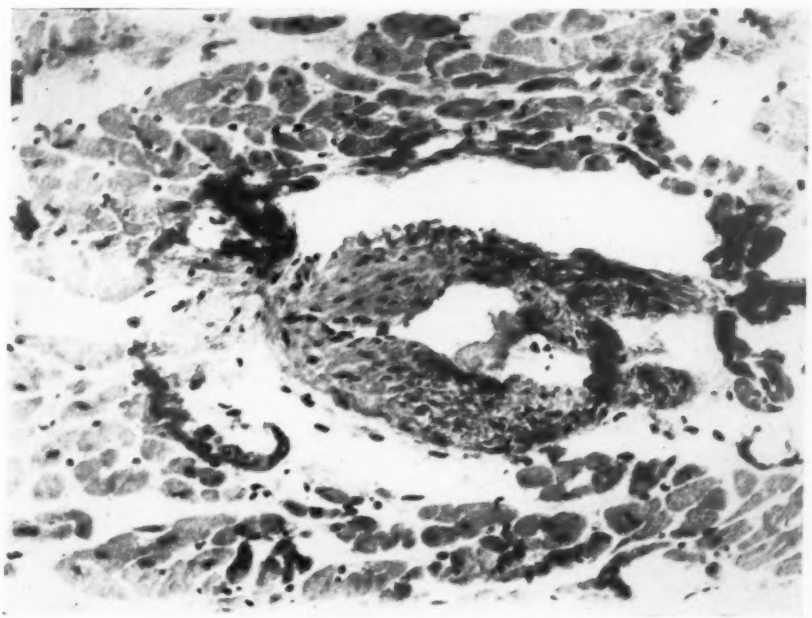


Fig. 5.—Section of myocardium and coronary artery, showing intimal thickening with narrowing of the lumen.

proximally in the same artery, a coronary accident, likely caused by rupture of a diseased and weakened vessel, resulted in sudden cardiac death. The possibility of thrombosis must also be considered, although no evidence other than the presence of a recent infarct (which may have been the result of hemorrhage) was found. It was decided to perfuse and inject this heart in the hope of demonstrating a thrombus and infarct. However, a well-developed collateral circulation made this difficult, and the fact (already mentioned) that the injection mass flowed freely into the infarcted area suggested that rupture of a coronary artery had occurred. Nevertheless, a loosely attached thrombus and weak vessel wall may have existed, but were not found after perfusion and injection. This experience strongly indicates that, when searching for evidence of coronary disease, such as thrombus formation, rupture,

etc., it is far better to dissect and section a heart carefully in the fresh state than to perfuse and inject the vessels.

It is interesting that the coronary artery distribution in this case was similar to that of the human heart. In many of the lower animals, particularly the dog, which is used a great deal in the experimental investigation of coronary occlusion, the distribution is significantly different from that in man. In the dog the right coronary artery is insignificant as compared to the left. The left coronary gives rise to both the anterior and posterior descending branches, and supplies the entire septum. In man and the ape the distribution of the right and left coronaries is of equal importance. The posterior descending is a branch of the right coronary artery, and the septum derives its supply from both the right and the left coronary arteries.

Since an experimental investigation of sudden coronary occlusion has been in progress in this laboratory for five years, the discovery of this case of fatal coronary thrombosis in the ape was of particular interest. After sudden ligation of a coronary artery in the conscious dog there are severe cardiac pain, cardiac irregularities, a fall in blood pressure, brief rigidity or convulsive movements, disappearance of pulse, congestion of neck veins, pallor, cyanosis, dilatation of the pupils, rigidity followed by muscular relaxation, a few deep gasps, and death of the animal. Therefore, it is interesting that in this case of coronary thrombosis in the ape the clinical signs were exactly comparable to those observed experimentally in the dog. Furthermore, published reports reveal that in human cases of sudden death caused by coronary artery occlusion the clinical signs and symptoms are also similar to those observed in the dog, and the nature of death is like that of the chimpanzee discussed in this paper. The pathologic observations were comparable to those in human cases of coronary thrombosis.

SUMMARY

An interesting case of coronary thrombosis in an 8-year-old female ape, in which the clinical signs, type of death, and pathologic changes in the heart were comparable to those in human cases of fatal coronary thrombosis, has been observed and described.

REFERENCES

1. Fox, H.: Diseases in Captive Wild Mammals and Birds, Philadelphia, 1923, J. B. Lippincott.
2. Cowdry, E. V.: Arteriosclerosis, New York, 1933, The Macmillan Co.
3. J. A. Campbell, Veterinarian to Toronto Zoological Gardens: Personal Communications.

Department of Reviews and Abstracts

Selected Abstracts

Green, H. D., and Wégria, R.: Effects of Asphyxia, Anoxia, and Myocardial Ischemia on the Coronary Blood Flow. Am. J. Physiol. **135**: 271, 1942.

The effects of systemic and myocardial asphyxia and anoxia on the coronary circulation of dogs anesthetized with morphine and sodium barbital have been studied by metering, with an optically recording orifice-meter, rate of flow of blood from the aorta into a coronary artery, while the aortic head of pressure was measured by an optically recording pressure manometer. Both of these instruments were of adequate frequency to record the details of the contour of the flow and pressure fluctuation occurring within a single heart cycle.

Asphyxia produced by interrupting the artificial respiration and local ischemia produced by temporarily stopping the blood flow to an area of the myocardium caused increased coronary flow even in the absence of any change of aortic pressure. Since the responses to hypercapnia were negligible under the conditions of these experiments, whereas the effects of systemic anoxia (produced by artificial respiration with mixtures of air and nitrogen) and myocardial anoxia (produced by cyanide injections into the coronary artery) were essentially similar, it is concluded that they all depend upon the anoxia produced and probably upon the presence of this anoxia in the myocardium.

Since the ratio of flow to pressure—index of flow—was increased even more in systole than in diastole, it is concluded that the anoxia causes a relaxation of the wall of the coronary vessels and also alters the dynamics of the myocardium in such a way that the systolic tension development in the myocardium is less effective in producing the extravascular compressing force normally present during ventricular systole.

AUTHORS.

Caviness, V. S., Bell, T. A., and Satterfield, G. H.: The Correlation Between Blood Pressure and the Concentration of Sulfocyanates in the Blood. North Carolina M. J. **2**: 585, 1941.

This study was undertaken to determine whether any correlation exists between natural blood sulfocyanate levels and blood pressure levels.

A total of 241 persons who had not received treatment showed (1) that each person has a fixed level of blood sulfocyanate which does not appear to change from week to week, (2) that natural blood concentrations of sulfocyanates range from 0.31 to 2.55 mg. per 100 c.c. of blood, and (3) that the average blood sulfocyanate level for each blood pressure group varies inversely with the blood pressure.

These findings suggest that sulfocyanates are the most important natural depressor substances in the human blood.

AUTHORS.

Cossio, P.: A New Model Stethoscope. Rev. argent. de cardiol. 8: 257, 1941.

A new model of chest piece for binaural stethoscope is described. It has the same size as those in general use and yet has a much greater amplifying power. The natural frequency of its resonating chamber may be changed at will, making it appropriate for the selective magnification of low- or high-pitched sounds.

After considering the characteristics of cardiac and pulmonary acoustic phenomena and the limitations of the ear, the author advocates the use of mediate auscultation in clinical study of the lungs as well as the heart.

AUTHOR.

Lieberson, A., Chasnoff, J., and Goldbloom, A. A.: Clinical Studies in Electrocardiography. IV. Value of Electrocardiogram in Coronary Thrombosis With Special Reference to Localization of Infarct. New York State J. Med. 41: 2032, 1941.

A correlative review of the clinical, electrocardiographic, and pathologic diagnoses was made in thirty-four patients (twenty-four men and ten women) who showed myocardial infarction at post-mortem examination. The autopsy material included sixteen cases of anterior infarcts, nine cases of posterior infarcts, and nine cases of combined anterior and posterior infarcts. Only sixteen of the thirty-four cases (47 per cent) were diagnosed by the electrocardiogram alone, the correct electrocardiographic diagnosis being made in eight cases of anterior infarct, seven of posterior, and one of combined infarcts. In the other eighteen cases the electrocardiogram did not show changes typical of infarction, but rather bundle branch or intraventricular block (eleven cases) and nonspecific myocardial damage.

In contrast, the clinical diagnosis before the electrocardiogram was taken was correct in twenty-six cases (76 per cent). When both the clinical and electrocardiographic evidence were used, the correct diagnosis of coronary infarction was made in thirty-one cases (91 per cent). The greater accuracy of the clinical as compared to the electrocardiographic diagnonis in these cases of proved coronary infarction emphasizes the prime importance of the history and clinical examination in the diagnosis of this condition, particularly in patients who suffer from old coronary thrombosis or sclerosis and who are not likely to have a characteristic electrocardiogram with the repeated infarctions.

AUTHOR.

Gillespie, J. E. O'N.: Pulmonary Venous Return Via the Superior Vena Cava. Brit. Heart J. 3: 241, 1941.

A case is described in which the only method by which blood could return from the lungs to the heart was through an opening into the superior vena cava. Communication with the left side of the heart was maintained by a patent foramen ovale.

It is believed that this abnormality has not been recorded previously.

AUTHOR.

Bramwell, C., and Jones, A. M.: Coarctation of the Aorta. The Collateral Circulation. Brit. Heart J. 3: 205, 1941.

The post-mortem findings in a patient with coarctation of the aorta who died from subarachnoid hemorrhage due to a ruptured cerebral aneurysm have been described.

As the coarctation had been diagnosed and the condition fully investigated two years previously, it was possible to compare the clinical and post-mortem findings.

Prior to autopsy the cadaver was injected with barium paste and the arterial anastomoses were studied radiographically.

The anatomy of the collateral circulation has been described. The factors that determine the distribution of rib notching and some possible causes of pain in this condition have been discussed.

AUTHORS.

Saphir, O.: Myocarditis: A General Review, With an Analysis of Two Hundred and Forty Cases. Arch. Path. **32**: 1050, 1941, and **33**: 88, 1942.

In an analysis of autopsy material comprising 5,626 cases, myocarditis was encountered in 240 cases (4.26 per cent). This material was taken from a general hospital, and no cases of contagious diseases were included. The more recent literature on myocarditis occurring as a disease entity or a sequela in infectious diseases is reviewed. Reports of fetal myocarditis are extremely rare. Myocarditis in contagious and infectious diseases, not necessarily associated with endocardial lesions, is discussed. Primary degenerative changes and secondary inflammation are found particularly in diphtheria, typhoid fever, and influenza (grip, "flu" and like conditions). Myocardial changes in scarlet fever are characterized by an involvement of the interstitial tissue, although the heart muscle fibers may also be replaced by inflammatory cells. Myocarditis occurring in instances of infection of the respiratory tract is discussed, myocarditis as occurring in pneumonia being stressed. Meager reference is also made to myocardial changes in measles, mumps, whooping cough, variola, varicella, paratyphoid, and dysentery.

Meningococcic myocarditis is characterized by a hemorrhagic exudate with the early appearance of endothelial leucocytes, destruction of muscle fibers, and presence of intracellular Gram-negative diplococci. Gonococcic myocarditis is often found in association with gonococcic endocarditis. Abscesses of various sizes may be present in the myocardium. Isolated involvement of the myocardium occurs in gonococcic infection. Myocardial changes are described in tularemia; the lesions are principally foci of necrosis with lymphocytic infiltrations.

The literature on isolated myocarditis is relatively extensive. Apparently the term "isolated myocarditis" denoted inflammatory changes in the myocardium of wide variety and of varied etiological background having in common an isolated and nonspecific involvement of the myocardium in the absence of inflammatory changes in the endocardium or pericardium and of unknown cause. Instances of isolated myocarditis may be divided into two groups—those in which there are more or less diffuse inflammatory lesions in the myocardium and those in which granulomatous lesions are present. Various etiological agents have been held responsible for these granulomas, and often syphilis or tuberculosis has been suspected but not proved to be the underlying condition. More recently a special form of hypersensitivity, particularly that due to arsphenamine, has been held responsible for this form of myocarditis. As long as the cause is not known the term "granulomatous" seems adequate. The diffuse form of isolated myocarditis is not characteristic histologically.

Myocardial lesions in association with subacute bacterial endocarditis are common. They consist of abscesses, diffuse acute inflammatory changes, particularly pronounced in the interstitial tissue and consisting mostly of infiltrations of polymorphonuclear leucocytes and lymphocytes, foci of perivascular infiltrations, and occasionally Aschoff bodies. Often minute organizing infarcts are encountered. Inflammatory changes are often present in the myocardium in instances of acute bacterial endocarditis. Foci of acute inflammatory changes, particularly pronounced in the interstitial tissue, are significant.

Although reports of abscesses of the myocardium are unusual, this study shows that such abscesses are common in instances of pyemia. Clinically they are regarded as occurring terminally. The clinical symptoms of myocarditis and the type of death of the patient probably depend upon the number and the localization of the abscesses.

Although the explanation of rheumatic fever as a form of allergy is attractive, it is at best a hypothesis founded on animal experiments. If rheumatic fever is to be considered an allergic phenomenon, the Aschoff body must be discarded as the specific histologic stigma of rheumatic myocarditis. Thus the significance of the Aschoff body has aroused much discussion in recent years. However, from a critical review of the literature and from studies of many hearts it appears clear that rheumatic myocarditis is a specific disease entity, probably caused by a specific though unknown agent, the Aschoff body being the characteristic granuloma. Structures which do not conform to the classic description should not be definitely classified as Aschoff bodies although they may resemble them. Aschoff bodies so far have not been produced experimentally. There seems to be not a single instance on record of Aschoff bodies in association with Sydenham's chorea in the absence of rheumatic fever.

Myocardial changes occurring in the Libman-Sacks syndrome are also discussed briefly.

In regard to tuberculous myocarditis, three main types are differentiated, namely, the nodular, the miliary, and the diffusely infiltrative. The last should be accepted only if the histologic changes are undoubtedly characteristic of tuberculosis or if the presence of the tubercle bacillus can be demonstrated either by guinea pig inoculation or by staining methods. Involvement of the myocardium in Hodgkin's disease, to judge from the literature, is apparently rare. Extensions of mediastinal masses into the pericardium and the myocardium are occasionally seen in routine post-mortem material, although such occurrences are not especially reported. Rarely may the myocardium be involved in Boeck's sarcoid.

From the available literature and from a study of this subject over a period of fifteen years it must be concluded that in acquired syphilis the entity syphilitic myocarditis, characterized by diffuse syphilitic inflammation and the presence of spirochetes, is extremely rare if it occurs at all. In congenital syphilis, however, myocardial lesions with the presence of spirochetes are occasionally encountered. Gummas are rarely seen. In a very recent report it was stated that gumma in the myocardium was encountered in only five of 30,265 autopsies.

The myocardium may be involved in blastomycosis, actinomycosis, moniliasis, and sarcosporidiosis. The respective parasites are occasionally encountered in the myocardium. Likewise myocardial lesions are reported in toxoplasmosis and histoplasmosis.

Typhus myocarditis is not rare. According to a recent report, 97 per cent of patients who died of typhus showed inflammatory lesions in the myocardium. Such lesions are usually focal, rarely diffuse. Myocarditis is also seen in Rocky Mountain spotted fever; occasionally Rickettsia-like bodies are found in large numbers in the myocardium. Rarely does yellow fever produce myocarditis.

Among helminthic diseases, trichinal disease is the one with which myocarditis is most frequently associated. The myocardial lesion usually occurs between the fourth and the sixth week following infection; at least death from myocarditis occurs at that time. Histologically, the lesion is characterized by an involvement of both the parenchyma and the interstitial tissue and by foci of necrosis. Among the inflammatory cells the lymphocytes predominate, but often many eosinophilic leucocytes are also present, although their occasional absence is stressed. From experimental studies and some autopsies on human subjects it is clear that larvae are present in

the myocardium about a week from the time of infection and that they then disappear. It is therefore evident that the diagnosis of trichinal myocarditis is not necessarily dependent upon the finding of larvae in the myocardium. Mention is also made of the involvement of the myocardium in echinococcus disease.

From a review of the literature one must conclude that there are no consistent myocardial changes described in patients dying with hyperthyroidism and hypothyroidism. So-called myxedema myocarditis does not occur. Myocarditis caused by acute or chronic nephritis per se or by uremia is a myth. Degenerative changes may be found in the heart muscle in such diseases, as in any wasting or chronic infectious disease. Such vascular changes as are seen in the kidney in arteriolosclerosis or arteriolonecrosis (nephrosclerosis of either variety) may also occur in the myocardium. Uremic pericarditis may extend into the myocardium. Whatever may have caused acute nephritis may also have caused myocarditis.

Myocardial changes are described in vitamin deficiencies. Most of the available references concern beriberi. The principal changes in the myocardium are of a degenerative nature, but there also occurs a type of inflammation described as "serious inflammation." This is thought to be a reaction of the tissues to the presence of plasma outside the capillary wall. The plasma apparently injures the tissues, with the result that there is a gradual new formation of a thin, lacelike connective tissue.

AUTHOR.

Moolten, S. E.: Prolonged Survival After Perforation of the Infarcted Interventricular Septum in Coronary Arterial Disease. Arch. Int. Med. **69**: 108, 1942.

Rupture of the left ventricle after infarction is immediately fatal unless the area of softening is situated in the interventricular septum. In the latter case death may be delayed several days and then occur as a result primarily of the severe shock and heart failure resulting from coronary occlusion. Prolonged survival is rare and is characterized by intractable right ventricular failure and the presence of the harsh systolic murmur of interventricular septal defect.

The interventricular septum considered as a functional entity is of particular significance, both as a component of deep muscle tracts common to both ventricles and as an agent for protecting the right ventricle by preserving the differential in pressure between the two ventricles.

AUTHOR.

Keagy, R. M., and Magee, R. S.: Supraventricular Tachycardia in Infancy. Pennsylvania M. J. **45**: 44, 1941.

A case of supraventricular tachycardia in a 5-month-old infant is reported. The acute attacks were treated successfully by the subcutaneous administration of mecholyl; recurrence of attacks has been prevented by daily doses of digitalis.

AUTHORS.

Epstein, E. Z., and Greenspan, E. B.: Rheumatic Pneumonia. Arch. Int. Med. **68**: 1074, 1941.

The authors have studied the problem of the pulmonary changes in rheumatic fever from a different aspect, choosing their cases in consecutive order, eliminating none of them because of the absence of clinical or macroscopic evidences of pneumonia or consolidation. In this manner the authors believe the evolution of the entire pulmonary picture may be unfolded in chronologic sequence and the histologic

changes correlated with the approximate duration of the disease as determined from the clinical history. They have ascertained the duration of the illness at home before admission to the hospital, the time spent in the institution before death, and the number of previous attacks of rheumatic fever, as well as the presence of chronic valvular changes from preceding attacks. This has enabled them to study the pathologic changes in the lung in relation to the acuteness and the duration of the rheumatic fever.

Forty-five cases of acute rheumatic heart disease were studied at autopsy and were divided into three groups on the following basis: (1) absence of previous history of rheumatic fever, no evidence of chronic valvular disease and an acute, rapidly fatal initial attack, (2) a previous history of rheumatic fever, evidence of chronic valvular disease and a rapidly fatal course in the last admission, and (3) chronic rheumatic cardiovalvular disease with the fatal attack lasting a considerable time.

The following conclusions were drawn. A specific rheumatic lung or rheumatic pneumonia cannot be considered to exist. Aschoff bodies were not found in a single instance. A characteristic, though not specific, pulmonary picture is present, which consists of alveolitis, marked congestion, edema, engorgement, and the formation of hyaline membranes. These lesions are considered to be a result of damage to the capillaries, with resultant alterations in vascular permeability. Vascular damage was likewise present in the main pulmonary artery and its branches and in the hepatic capillaries. This vascular change corresponds to the involvement seen in the arterial tree in various organs of the body in acute rheumatic fever.

AUTHORS.

Glazebrook, A. J., and Thomson, S.: The Pulse Rate in Acute Juvenile Rheumatism. Edinburgh M. J. 68: 619, 1941.

A pulse depression was found to be a common feature of the first attack of rheumatism in adolescents and young men. It occurred at an early stage and was often of a transient nature. Its recognition may aid diagnosis. It appeared to afford an index of the severity of the toxemia. It was associated with a marked sinus arrhythmia and sometimes progressed into a temporary partial heart block. A similar depression was seen in streptococcal infections which are possibly closely allied to the rheumatic state. The prognostic significance of a pulse depression as regards permanent cardiac damage was considered to be bad.

AUTHORS.

Page, I. H.: The Nature of Clinical and Experimental Arterial Hypertension (the Edward Gamaliel Janeway Lecture). J. Mt. Sinai Hosp. 8: 3, 1941.

The development of knowledge of experimental hypertension, the relation of hypertension to vascular changes in the kidney, and the present conception of clinical hypertension are reviewed. The action of renin and angiotonin is described, and the evidence for the existence of a pressor-inhibition and its usefulness in the treatment of essential and malignant hypertension is presented.

MCCULLOCH.

Naide, M.: The Causative Relationship of Dermatophytosis to Thromboangiitis Obliterans. Am. J. M. Sc. 202: 822, 1941.

A study has been made of patients with thromboangiitis obliterans with regard to the possibility that the disease may be caused or precipitated by fungi which cause dermatophytosis. While evidence has been presented suggesting an etiological relationship between the two diseases, it is insufficient, at present, to be

conclusive. Nevertheless, certain clinical features of thromboangiitis obliterans are more readily accounted for on the basis of fungous infection than by other etiological agents thus far proposed. It therefore seems of primary importance to look for and to treat persistently any evidence of dermatophytosis in the patient with thromboangiitis obliterans.

AUTHOR.

Davies, D. H.: Idiopathic Cystic Medial Necrosis of the Aorta. Brit. Heart J. 3: 166, 1941.

A case of idiopathic cystic medial necrosis of the aorta, without rupture, has been reported. The presenting signs were those of aneurysmal dilatation of the aorta with aortic incompetence and terminal left ventricular failure.

AUTHOR.

Mason, J. M.: The Treatment of Vascular Injuries. Ann. Surg. 114: 191, 1941.

The treatment of vascular injuries is discussed under the following headings:

1. The great improvement in the treatment of shock and hemorrhage brought about by developments in transfusion since the World War.
2. Classification of vascular injuries in regard to treatment:
   a. Those which demand immediate treatment.
   b. Those in which a brief period of delay is permissible.
   c. Those which come under observation at a late period.
3. Dangers inherent to ligation of arteries, especially in patients already exsanguinated.
4. Measures for increasing the safety of ligations.
5. Traumatic aneurysms and arteriovenous communications.
6. Wounds of the heart.
7. Vascular injuries in the current war.
8. Experience in civil practice.

AUTHOR.

Banks, B. M.: Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? New England J. Med. 225: 433, 1941.

Clinically, there are characteristic syndromes that correspond to the diagnostic terms of scleroderma, dermatomyositis, disseminated lupus erythematosus, and polyarteritis nodosa. Not infrequently, however, patients present symptoms and signs that form essential characteristics of two or more of these conditions.

Since the diagnosis is almost always a clinical one without laboratory confirmation, the placing of undue emphasis on certain features may lead to diagnostic errors and a tendency to identify one disease with another.

There is no uniformity of opinion regarding the specific and fundamental pathology of certain of these syndromes, all of which represent a widespread vascular involvement, differing usually in the extent of the pathologic change, the size of the vessels involved, and the organs chiefly affected.

AUTHOR.

Takats, G. de: Management of Peripheral Vascular Disease. Illinois M. J. 80: 307, 1941.

A simple classification of peripheral vascular disease is presented by grouping vascular occlusions into acute, chronic, organic, functional, inflammatory, degen-

erative, vasospastic, and vasoparalytic occlusions. The purpose of an examination of the peripheral vascular status is to determine these various elements in the individual case and to estimate the capacity of the vascular bed. The objectives of treatment have been summarized under three headings, namely, the improvement of collateral circulation, the alleviation of pain, and the removal of nonviable parts in the optimal time and level. Methods of treatment are discussed under physical, medical, and surgical methods. An intelligent coordination of these procedures will yield the best results. The use of heat should be limited to the root of the limb, and the affected limb should be wrapped in cotton and kept at room temperature. Alternate hot and cold baths have not been used, but warm sitz-baths are recommended. Postural exercises, massage, and diathermy are discussed briefly. The use of sodium chloride by iontophoresis has given encouraging results in softening of sclerodermic and thrombophlebitic indurations. Alternate suction and pressure therapy has been given a thorough trial on ambulatory patients, and it was found that the degree of involvement present at the onset of the treatment determines the benefit one may expect from such therapy. Intermittent venous hyperemia has been used to a great extent; many patients used it at home for several months and years. The mechanical filling and stretching of the vascular tree undoubtedly helps to develop a collateral circulation. The author has not been able to find any difference between the clinical results obtained by this method and the suction and pressure treatment.

The object of drug therapy in peripheral vascular disease is to dilate the peripheral vascular bed. This can be obtained by measures producing central vasodilation through fever or by direct action on the smooth muscles of the blood vessels. Typhoid vaccine has been used to a great extent, but fever- or chill-producing doses have been avoided and only subreactionary doses have been given. Only patients with inflammatory lesions have been given typhoid vaccine. Hypertonic solutions have not been used, but sodium chloride can be given by mouth in 10 to 15 gr. tablets. Diets low in potassium accomplish the same effect. Alcohol is permitted and encouraged for those who are accustomed to taking it in moderate doses. Abstinence from tobacco is insisted upon in Buerger's disease and less rigidly enforced in arteriosclerotic patients. Theocalcin is used in the arteriosclerotic group because of its favorable action on impaired coronary circulation. Its effect on the peripheral vascular bed is doubtful when given in the customary doses by mouth. Papaverine is used in ½ gr. doses and is given intravenously in early cases of embolism and acute thrombosis. Nitrites and choline derivatives have been used extensively. Iodides, given intermittently to arteriosclerotic patients and to patients with Buerger's disease, are still being continued mainly on an empirical basis.

The indications for sympathectomy in peripheral circulatory disturbances have been summarized. The causes of failure, which are so often emphasized, are readily found in incomplete operations and improper selection of cases. The properly selected case derives great benefit from this operation. The use of paravertebral block with procaine in acute vascular occlusion and the indications for paravertebral block with alcohol are discussed. A peripheral nerve block in the presence of continuous intractable pain has a small but important part in the treatment of peripheral vascular disorders. When parts of the extremity are irrevocably lost or endanger life by absorption or spreading infection, amputation should not be delayed. The proper level of amputation must be determined by the level of adequate circulation and in consideration of adequate weight bearing. The technique of amputations today is such that these are now delicate, plastic operations performed under low spinal anesthesia and with a low mortality. The rehabilitation of amputated patients should and can be successfully undertaken.

AUTHOR.

Ravdin, I. S., and Wood, F. C.: The Successful Removal of a Saddle Embolus of the Aorta, Eleven Days After Acute Coronary Occlusion. Ann. Surg. **114**: 834, 1941.

A physician, aged 32 years, suddenly developed symptoms and signs which led to the clinical diagnosis of cardiac infarction in the anterior surface of the left ventricle. While at rest in the hospital on the eleventh day, he awoke with an agonizing pain in both legs with coldness and mottling. He himself made a correct diagnosis of an embolus at the bifurcation of the aorta. At the operation the embolus was removed successfully. The patient made an uneventful recovery and is well after more than a year.

Immediately after the embolectomy, novocain was injected into the left paravertebral sympathetic plexis for nerve block to relieve vascular spasm distal to the arterial obstruction. Heparin also was given for eleven days following operation to prevent distal propagation of a thrombus.

The author believes that embolectomy is not always necessary in major arterial obstruction. The decision depends on whether or not there is evidence of continuing improvement in circulation. If this fails to occur, operation should be carried out, for, after three to five hours, changes in the intima at the site of the occlusion may result in further thrombosis, despite the use of heparin, following the closure of a vessel.

McCULLOCH.

Payne, R. T.: The Scope of Operation in Treatment of Varicose Veins. Brit. M. J. **2**: 533, 1941.

The adequate treatment of primary uncomplicated varicose veins involves the complete obliteration of the varicose circulation.

Injection treatment will secure this in most cases; but operation, or more often a combination of operation and subsequent injections, is necessary for some cases, particularly the more advanced ones.

No case is too severe for the combined treatment.

The absolute and relative indications for operative treatment are given.

The details of preoperative treatment, operation, and postoperative care are described, and subsequent injection treatment is outlined.

The whole varicose circulation can be obliterated completely in six to eight weeks from the time of operation, and the patient rendered fit even for heavy work.

Patients with the severe type of varicosity should be examined at intervals of one year whenever possible.

The factors governing prognosis are outlined. Of the controllable factors, the most important is the completeness of the obliteration of the varicose circulation.

AUTHOR.

Ciocco, A., Klein, H., and Palmer, C. E.: Child Health and the Selective Service Physical Standards. Pub. Health Rep. **56**: 2365, 1941.

The main purpose of this inquiry was to determine whether in childhood there were appreciable indications of the defects that have brought about the present disqualification of selectees. For this purpose an attempt has been made to compare, for each disqualifying cause, the childhood status of men who were rejected because of this cause with that of men who successfully passed the physical examination.

Twenty-seven selectees were disqualified because of some impairment of the cardiovascular system; records of school physical examinations and medical histories were available for twenty. At the time of the school examination some form of cardiac

abnormality was recorded for seven, or about one-third of the twenty men. Loud murmurs were noted for three, including one whose heart was said to be enlarged. A fourth was alleged to have "heart disease"—without further elucidation—and tachycardia was reported for a fifth. There was a history of rheumatic fever for two other selectees. Among the 149 selectees in Class 1-A for whom childhood physical examination records are available, none was stated to have any involvement of the cardiovascular system at the time of the school examination.

Since the study deals with a relatively small sample, perhaps too much weight should not be attached to the fact that seven of twenty young adults rejected for heart disease had, as children, some manifestation of rheumatic fever or cardiac symptom at the examination made in school, while no such sign was observed at the corresponding examination of the present-day selectees of Class 1-A. However, it must be recalled that, as is usually the case in school examinations, none of the records is sufficiently descriptive to give detailed information regarding the actual status of the heart muscle and function at the time.

AUTHORS.

White, P. D.: The Soldier and His Heart. War Med. 1: 158, 1941.

The author discusses briefly the problems relating to the heart which confront the draftee and the examining and classifying boards. In an appendix he gives the regulations concerning the heart, blood vessels, and the circulation from the standards of a physician's examination during the mobilization issued by the War Department in 1940.

McCULLOCH.

Master, A. M.: Effort, Trauma, Occupation and Compensation in Heart Disease. Bull. New York Acad. Med. 17: 778, 1941.

The relation of effort, occupation, and trauma to heart disease frequently offers a difficult problem, and each case must be carefully considered.

Symptoms may be due to pre-existing heart disease and the effort or trauma coincidental. Yet effort and trauma may aggravate previous heart disease. Effort does not damage a normal heart.

The effort is significant if it is unusual and not routine, and if symptoms arise immediately or soon after. The latter is also true of trauma.

A "stroke" may occur in the course of hypertension and arteriosclerosis. It is probably not related to effort, but the effect of trauma cannot be excluded.

Heart failure usually is a result of progressive heart disease and may be induced by infection. Only rarely is it precipitated by exertion, but the latter may aggravate it.

Angina pectoris is associated with coronary sclerosis. Individual attacks may be related to effort or trauma but later attacks or a persistent anginal syndrome rarely is.

Effort, occupation, and trauma play no role in coronary occlusion. The opposite view is often based on a confusion of coronary occlusion with the syndrome of angina pectoris, preliminary pain in coronary occlusion, and contusion of the heart.

Coronary insufficiency usually occurs in association with coronary sclerosis and may be related to effort and trauma.

Rheumatic fever rarely if ever is precipitated by effort or trauma.

Aortic aneurysm due to syphilis or sclerosis is not produced by effort or trauma. In rare instances effort or trauma may lead to rupture or to dissecting aneurysm.

Trauma may produce commotio cordis and contusion of the heart. In addition, the heart, large vessels and, in very rare instances, a valve may be ruptured.

Trauma does not produce coronary occlusion, and it probably does not lead to a persistent anginal syndrome.

Trauma may be the result, and not the cause, of heart disease.

Subacute bacterial endocarditis is not causally related to trauma with infection, but acute bacterial endocarditis sometimes is.

Cardiac irregularities may be induced by effort or trauma.

Carbon monoxide poisoning occasionally results in damage to the heart, or aggravates a pre-existing condition, but it does not lead to coronary occlusion. Most cases of cardiac involvement attributed to carbon monoxide are based on insufficient evidence.

While neurocirculatory asthenia usually occurs in persons constitutionally susceptible to strain, in rare instances the onset of symptoms may be related to effort or trauma.

The problem of compensation in heart disease would be simplified considerably if a completely trustworthy history could be obtained in every case.

AUTHOR.

Battro, A., Segura, R. G., and Lanari, A.: The Action of Hypertensin in Normal and Hypertensive Subjects. Rev. argent. de cardiol. **8**: 250, 1941.

The intravenous injection of hypertensin (1 unit per 10 kg. weight) in fourteen normal and nine hypertensive subjects produced a rise in systolic (average 36.4 and 32.7 mg. Hg, respectively) and diastolic (average 31.7 and 26.6 mm. Hg, respectively) blood pressure lasting five to nine minutes. Previous injection of atropine increased and prolonged the pressor action of hypertensin. No changes occurred in the ventricular complex of the electrocardiogram.

The injection of hypertensin into the brachial artery was followed by a marked reduction of the oscillometric index which persisted for thirty minutes in one case.

No relation between sensitivity to the cold test and to the pressor action of hypertensin was found in hypertensive patients.

AUTHORS.

Book Reviews

CLINICAL ELECTROCARDIOGRAPHY: By David Scherf, M.D., and Linn J. Boyd, M.D., Associate Clinical Professor of Medicine, and Professor of Medicine, respectively, New York Medical College, Flower and Fifth Avenue Hospitals. The C. V. Mosby Co., St. Louis, 1941, second impression, 362 pages, 207 figures, $7.50.

This brief work on electrocardiography is a satisfactory introduction to the subject. It serves a purpose in acquainting the beginner in this field with the fundamentals of electrocardiography. There are now a number of good works on electrocardiography, and each will occupy its own position. This book is not encyclopedic but does include the majority of the accepted interpretations. The work is predominantly continental in its viewpoint and is to be recommended.

HAROLD FEIL.

TRASTORNOS CARDIACOS EN LOS ESTADOS ANEMICOS: By Dr. Eugenio R. Pietrafesa, Libreria y Editorial "El Ateneo," Buenos Aires, 1941, 207 pages, 127 illustrations.

As indicated by the title, this book presents a clinical and experimental investigation of cardiac disturbances in anemic states. The author studied twenty cases of severe anemia in which there were signs and symptoms related to the heart and blood vessels. Heart murmurs, arterial and venous murmurs, anginal pain, changes in the size of the heart, and electrocardiographic abnormalities were investigated. Experimental attempts to reproduce the electrocardiographic changes shown by anemic patients are reported, and histologic sections of the heart muscle of the experimental animals are discussed.

The heart murmurs are explained as the result of either increased velocity of blood flow or functional insufficiency of valves caused by cardiectasis.

Anginal pain was present in only a small percentage of cases and is attributed to coronary insufficiency caused by low oxygen tension of the blood.

The heart was enlarged in all cases. This enlargement was reversible, and was due to dilatation of the ventricles. In some cases there was also dilatation of the pulmonary artery, and, in others, of the left auricle. These phenomena are attributed to the effects of coronary insufficiency on the heart muscle.

The electrocardiograms showed low voltage of QRS and of the T wave, downward displacement of the S-T segment in Leads I and II, and, less often, changes in the P wave. The author ascribes these abnormalities to coronary insufficiency caused by the anemia.

Dyspnea, palpitation, sinus tachycardia, extrasystoles, splitting of the second heart sound, gallop rhythm, and hypotension were observed; all of these disappeared when the condition of the blood improved.

The author discusses the question whether anemia may cause congestive heart failure, with or without angina pectoris, as some have maintained. Four of his patients had congestive failure and recovered completely when their anemia was treated with iron or liver. Digitalis had no effect in these cases.

The experimental work was done on rabbits. They were bled repeatedly and exercised. Their electrocardiograms showed changes which were similar to those encountered in patients with severe, chronic anemia, and this tended to substantiate the idea that coronary insufficiency is the cause of these changes.

The book is well written and well printed. The author cites many previous studies, and it is sometimes difficult to separate his data from those of others. Detailed clinical reports and three indexes are included.

ALDO LUISADA.

Erratum

In the March issue of the JOURNAL, page 333, Dr. Miller's discussion of the article "The Induced Anoxemia Test" by Clough Turrill Burnett, M.D., Marshall Grant Nims, M.D., and C. J. Josephson, M.D., should read:

DR. H. R. MILLER, New York, N. Y.—Dr. Burnett's excellent studies raise the question—and I hope Dr. Burnett will comment on this—whether, in subjecting the normal subject to a lowered arterial oxygen saturation, we are dealing with an effect of deprivation of oxygen of central autonomic nuclear masses, or of the heart, or perhaps with both factors. The reactions noted by Dr. Burnett would seem to indicate that central antonomic controls of the cardiovascular apparatus were involved. It is now recognized by physiologists that various levels of the brain have an optimal reaction in accordance with the quantity of oxygen made available for their utilization.

The second point I have in mind is the matter of syncope in association with cardiovascular states. It is a commonplace that, when there is cardiovascular depression, syncope is very likely to occur, but syncope may also occur without cardiovascular depression. Stimulation of certain areas of the brain may produce marked signs of cardiovascular depression, but no syncope. On the other hand, stimulation of such a trigger zone as the carotid sinus area is known to cause marked circulatory depression, often with syncope, but, at times, without this depression. These results, it seems to me, direct our attention to an interesting point. Is there a separate mechanism responsible for syncope? In other words, when syncope takes place as a result of either central or peripheral excitation or inhibition, and in the absence of cardiovascular features, are we dealing with a mechanism which is independent of the autonomic regulation of circulation?

In the kind of test studied by Dr. Burnett and his co-workers the normal subject may be reacting primarily by virtue of some change in his heart muscle, or the cardiac effect may be only a localized expression of a much more extensive autonomic effect. If we, as clinicians, are to employ a test of this character, we must be certain that the effect is chiefly and primarily on the heart, and not widespread and generalized.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. PAUL D. WHITE
President

DR. ROY W. SCOTT
Vice-President

DR. T. HOMER COFFEN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

*DR. EDGAR V. ALLEN	Rochester, Minn.	*DR. EDWIN P. MAYNARD, JR.	Brooklyn
DR. T. HOMER COFFEN	Portland, Ore.	*DR. THOMAS M. McMILLAN	Philadelphia
DR. CLARENCE DE LA CHAPELLE	New York City	DR. JONATHAN MEAKINS	Montreal
DR. HUGH FARRIS, St. John, N. B., Canada		DR. E. STERLING NICHOL	Miami
DR. NORMAN E. FREEMAN	Philadelphia	DR. FRANKLIN R. NUZUM	Santa Barbara
DR. TINSLEY R. HARRISON,	Winston-Salem, N. C.	*DR. ROY W. SCOTT	Cleveland
DR. GEORGE R. HERRMANN	Galveston	DR. FRED M. SMITH	Iowa City
DR. T. DUCKETT JONES	Boston	*DR. HOWARD B. SPRAGUE	Boston
*DR. WILLIAM J. KERR	San Francisco	DR. WILLIAM D. STROUD	Philadelphia
DR. EMANUEL LIBMAN	New York City	*DR. PAUL D. WHITE	Boston
DR. DREW LUTEN	St. Louis	DR. FRANK N. WILSON	Ann Arbor
DR. GILBERT MARQUARDT	Chicago	*DR. IRVING S. WRIGHT	New York City
*DR. H. M. MARVIN	New Haven	DR. WALLACE M. YATER	Washington, D. C.

DR. H. M. MARVIN, *Chairman, Executive Committee and Acting Executive Secretary*
ANNA S. WRIGHT, *Office Secretary*
TELEPHONE CIRCLE 5-8000

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of twenty-seven eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

**Executive Committee.*